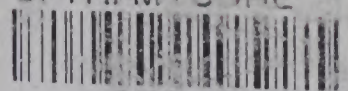


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MODERN PHARMACOLOGY AND THERAPEUTIC GUIDE

A comprehensive Text-Book of combined Clinical and Systematic Medicine containing in clear and compact form all latest items of Bed-Side Case-Taking and Diagnostic Methods, physical and laboratory, along with detailed consideration of the Diseases of the various Systems in their etiology, pathology, symptomatology, physical signs, differential diagnosis, prognosis and treatment with suitable prescriptions. Diseases special to ladies and the Tropics as a whole are taken up separately.

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With Recent Therapeutic Advances.

MODERN PHARMACOLOGY AND THERAPEUTIC GUIDE

(According to British Pharmacopœia 1948 with Addendum 1951 and
Indian Pharmacopœial List 1946 with Non-official, Indigenous
and Proprietary Drug Preparations.

BY

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UNIVERSITY OF CALCUTTA.



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अनन्तशास्त्रं बहुवेदितव्यं
स्वल्पश्च कालो बहवश्च विघ्नाः ।
यत्सारभूतं तदुपासितव्यम् ॥

The Sastras (books of knowledge) are endless and much is to be learnt, but the time (life's time) is short and obstacles are many. Therefore the essence (of these) should be adored. UTTARGITA III, in BRAHMANDAPURANAM.

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PREFACE TO THE NINTH EDITION

Pharmacological Researches are making such rapid forward march that since the publication of the last edition in September 1948, many new drugs and special preparations have been introduced in practice. The Pharmacopœia Committee in England had to publish *Addendum 1951*, in September last. A vast mass of literature has consequently accumulated and we have tried our best to summerize these and incorporate in the present edition in clear, practical and easily assimilable form.

From the beginning, Modern Pharmacology and Therapeutic Guide took up a special line, that of making up a practical hand-book of the essential items covering the needs of the *students* of Pharmacy and Medicine and of the busy *dispenser* and a *practitioner* of *General Medicine*. Author's long experience in clinical teaching and in practice of Medicine gave fairly clear indications of the need and helped to make up the book in the present form.

The *Pharmacists' portion* covers 65 pages in one place and more in the body of the book. This portion is also in the curriculum of the *preclinical portion* of the students of Medicine. This has special chapters on incompatibles and on more recent methods in dispensing especially of the hydrophilic ointments and skin creams: these will be useful to a busy dispenser also.

But much more important is the clinical portion or *Therapeutics* which is in the curriculum of the Senior Medical Students. Being a part of and intimately correlated to Medicine and Pathology, this forms the basis of medical treatment. As before, the therapeutic application of a drug immediately follows the principles of drug action in the same running lines separated only by parenthesis. This causes more vivid appeal, saves time of the readers and economises space. This section on *Drug action* has been carefully revised, amplified and in many places rewritten. A *summary* has been added under each to emphasize the leading items.

The drug action has been illustrated by *prescriptions*, whose number in this edition reaches 500 and also by reference to the *commercial preparations* available: their number exceeds 700. Most of the drugs newly admitted into the British Pharmacopœia have been marketted in special trade names and these even more recently introduced, very useful but not yet official, are only in trade names. A directory of these names is thus essential for clinical practice: these have been carefully selected and introduced.

To help *practical clinical application*, these have been indexed under 210 *diseases*, adequately covering the daily medical practice. A busy general practitioner quickly gets in touch with the various drug combinations and the relevant commercial preparations available and by referring to the text of the book, makes a more accurate selection with minimum effort. A medical student for the final examination, masters his item of medical treatment with greater ease and precision.

The existing section on *Diet* with methods of preparation of *invalid food* and calorific and vitamin *values of food* commonly used in this country has also been carefully revised.

We have obtained popularity for the new style we adopted and we have in this edition more carefully and intensively gone further ahead. The reading matter has consequently increased inspite of more compact printing and removing from the book those items that are no longer so essential in clinical practice. We have thus persisted in our scheme of *maximum substance in minimum space at moderate cost*. We hope this edition will be found more useful both to the students and general practitioners.

A. R. MAJUMDAR

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MODERN PHARMACOLOGY

AND

THERAPEUTIC GUIDE

INTRODUCTION

The primary instinct of the primitive human being grouped in different parts of the world, was of self-preservation and propagation. They evolved certain convenient codes of ethics which afterwards developed into theology and religion. Through these they made arrangement for an orderly growth and maintenance of internal peace. They also sought relief from mental and physical distresses. The latter known as *diseases* have thus been in existence from the beginning of human habitation. In addition to prayers, benediction and charms, physical means as *drugs* were also searched for as the means of cure. The first system of medicine was naturally very crude, consisting of the use of herbs and various mineral and animal products that were available in the nearest surrounding. These were often kept strictly secret by individuals, families or tribes. Subsequently, along with the progress in other departments of human knowledge, the knowledge of medicine also advanced and a medical profession came into existence. It is very likely that before the Aryans left their common primitive home, to spread over the different parts of the world, some written codes of medicine must have evolved.

The first systematic treatise on medicine was undoubtedly the *Ayurveda* in India and that is at least 500 years ahead of the Greek Medicine. This is dated 1000 to 1500 B.C. Several of the authors of books on Philosophy and Theology were writers of medical books also and so the early medical literatures were related to metaphysics and belief in supernatural agencies as the cause and curer of diseases. Thus in India this was originally a part of the fourth Veda, called the *ATHARVA VEDA*. But the real father of Indian Medicine was *ATREYA* with his distinguished disciples, *AGNIVESA*, *BHELA*, *JATUKARNA*, *PARASARA*, *HARITA* and *KSHARAPANI*. Works of *BHELA* and *HARITA* are still available in fragments and those of *AGNIVESA* were edited by *CHARAKA*, which stand unsurpassed as a standard and authoritative book on *Ayurveda* even to-day. Other works are yet untraced.

The next outstanding personality in Indian Medicine was SUSRUTHA whose works, in points of antiquity and scientific value, stand only second to CHARAKA. He made further progress in the medical knowledge and described, in addition, many surgical instruments and techniques which may rightly claim to be the pioneers of this branch.

In Greek Medicine also, the earliest medical writer was a philosopher, PYTHAGORAS, who lived in about 600 B.C. He was a great traveller and had been to India and Egypt, the two most distinguished centres of learning of that age and it is only natural that the knowledge of these two countries must have considerably influenced him. But the real father of Greek Medicine was HIPPOCRATES, born in about 460 B.C.

Near about the time of Alexander the Great, the Greeks came in greater contact with India and this was not only followed by a historical matrimonial alliance between the Greek Princess Helen and Indian Emperor Chandragupta representing the two principal pioneers of human civilization but also a considerable interchange of thought, both philosophical and scientific. Henceforth both the Hindu and the Greek Medicines flourished side by side. But when the Greeks finally left India, any communication between them became increasingly difficult and later on a more or less independent system of medicine developed in the two places.

The Indian system of medicine received considerable impetus during the Buddhist period especially of Emperor Asoka and the two most distinguished personalities of that age were NAGARJUNA and VAGBHATTA. The whole country was studded with numerous hospitals and dispensaries and so an elaborate pharmacopœia and pharmacy developed with innumerable "official" prescriptions.

Although a few metallic preparations are mentioned both in CHARAKA and SUSRUTA (1000 to 500 B.C.), from the time of VAGBHATTA (200 A.D.), more of these came into prominence. Later VRINDA (900 A.D.) and CHAKRAPANI (1066 A.D.) introduced a large number of heavy metals in therapeutics. The search for means of physical well-being brought in a desire for immortality and also to find out much longed for philosopher's stone which by touch would transform everything into gold. These brought into existence chemistry (*Kimia*, transmutation) as an essential side-track of medicine. Later still, in Tantric (1100 to 1300 A.D.) and Iatro-chemical periods (1300 to 1550 A.D.), further progress was made, especially in chemistry which reflected on the contemporary medical knowledge.

In later days, the growth of Indian Medicine was largely handicapped for three reasons. (i) Owing to an aversion for touching dead bodies, anatomical and pathological postmortem examinations were not done to any large extent and so a symptomatic system of medicine only developed. (ii) The best

brains of the country kept away from the medical profession, they more commonly taking up politics or metaphysics and theology as their career. (iii) Uncertain political state of the country and frequent invasions from outside were unfavourable to progress of knowledge by research. So all the writers on Indian Medicine who followed the illustrious pioneers in later ages, were mainly annotators and compilers of old works and not so many original authors of that high order.

Yet, taking the ancient Indian Medical Literature as a whole, it must be admitted that it has in it a system of medicine with many pharmaceutical preparations of surprisingly high curative value. It would be of immense economic gain to the country to investigate these preparations with an open mind and scientific outlook and to separate *facts* from *traditions*. A few of these drugs are already in the British Pharmacopœia, many are effective substitutes of the B.P. products, some of these have been incorporated in the Indian Pharmacopœial List 1946 and with a painstaking research, many more are likely to be found out.

In the early part of the ninth century A.D., the Arabs had the treatises of Hindu and Greek Medicines translated into Arabic and this formed the nucleus of the Unani Medicine. By the orders of Caliphs Harun and Mansur, several standard works of Indian Medicine were translated and Charaka, Susruta, Nidana and Astanga (of Vagbhata) were known as SARAK, SUSRUD, BADAN and ASANKAR in Arabic. Rhazes (852 to 932 A.D.) and Avenzoar (980 to 1037 A.D.), the two luminaries of Unani Medicine, had no less of Indian influence than Greek. Afterwards with the fall of the Greeks and the Romans, the Saracens became a very prominent power in the West, they being established in a large part of Southern Europe with the distinguished intellectual centre at Cordova in Spain; the medical knowledge of the East was carried to Europe and flourished. But it was not until the beginning of the sixteenth century that real birth of Modern Medicine was signalled and in this the principles of the Indian and Unani Medicines were the essential basic factors.

Henceforth a new era began. The research in various departments of medicine for a long time lying nearly dormant, being partly chained by usages and superstitions, began to break through all barriers.

The progress, to start with, was rather slow but within the last half a century by the combined efforts of workers, too numerous to mention, from many parts of the world, so large a ground has been covered up and this is going on with such an increasing speed that rationalism in therapeutics based on logical data is on a firm footing and many diseases, so long believed to be incurable or are starting in formidable epidemics, are being brought under control and many drugs obtained from natural sources in limited amount from a

particular part of the world only, are now being synthetised, available in much larger quantity at less cost.

THE PHARMACIST AND PHARMACOPŒIA

It is obvious that in the early stages, the physician himself had to find out his own crude medicinal requisites and make these into a form according to his liking, suitable for administration to the patient. With advancement of chemistry and greater medical knowledge, skilled druggists as a class, distinct from the physicians, came into existence, they being the *pharmacist* or persons to take up the work of manufacture and storage of various medicinal preparations designated as *drugs*.

The State then came forward to co-ordinate by check and guidance the different druggists so as to fix up a definite standard of the drugs and direct their manufacture in a particular way so that the prescriber could be assured that by ordering a specified preparation, all druggists would give him the identical stuff.

The official book describing these methods is called the **Pharmacopœia** (*G. pharmakon*, a drug and *poies*, to make) and all the drugs described therein are the “official” preparations. This book is slightly different in different countries and is revised periodically in order to keep it up to the recent developments of pharmaceutical and therapeutic knowledge. In India, the book prescribed by the British Government, under the direction of the General Council of Medical Education and Registration (the first publication was probably in 1864), is current, the last publication being in 1948. Any drug prepared according to the above is called a B.P. preparation.

An Indian Pharmacopœial List has been published (1946) apparently as a supplement.

In this way, the knowledge of *identification* of drugs, their *collection* from different sources and their scientific *grouping*, their *preparation* into forms suitable for administration to the patient and lastly their *actions* in health and in diseases became specialised into separate branches. The first of these is called the *Materia Medica* proper (also called *Pharmacognosy*),—dealing with the origin, source, distribution, identification and collection of drugs. The second is called **Pharmacy** describing the composition and preparation of remedies employed in medicine, either “official” in the *Pharmacopœia* or made up according to a prescription from a qualified medical practitioner. The third is **Pharmacology** including **Therapeutics**: this is the science dealing with the experimental study of the action of drugs upon normal healthy animals and human being and their application in different conditions of diseases. Certain drugs given in excess and certain others with powerful action but of no therapeutic value when taken internally, act as *poisons*. Diagnosis of poisoning (including their detection)

and treatment form an additional subject and is called **Toxicology**.

Therefore, for the proper understanding of the principles of *Materia Medica* including *Pharmacy*, a fairly good knowledge of Physics and Chemistry and also of Biology is essential and for *Pharmacology* and *Toxicology*, that of Physiology, Biochemistry and Pathology including Bacteriology are necessary. *Therapeutics* are more or less integral portions of Medicine, requiring for their proper appreciation a fair knowledge of the causation and pathology of diseases.

DRUG ACTION

The modern investigations on the action of drugs are carried on by observing the effects when these are

- (1) Administered to living animals healthy or diseased :
- (2) Applied on the isolated organs or other tissues of certain animals also on various infecting organisms.
- (3) Investigation through radio-active isotopes and by electron microscope.
- (4) Also administered to a human being in health and in disease for therapeutic purpose.

Where a Drug Acts

(1) A drug may act, **LOCALLY**, exactly on the tissues it comes in intimate contact with, either on the superficial epithelia of the skin, mouth, stomach, intestine, eyes, upper respiratory passages, genito-urinary tracts or other parts of the body where the drug can have direct access (also called direct or *topical action*). This is manifested on the epithelia of contact, nerve endings or on the blood vessels. Sometimes the local effects of one place are manifested in another place through nervous influence. Thus bitters or acids placed in the mouth favour reflex secretion of gastric juice : an irritant acting on the skin causes circulatory effects. These are *reflex* or indirect drug action.

(2) **AFTER ABSORPTION INTO THE CIRCULATION**.—This is called the *specific selective* or *systemic action* of the drug. This specific effect is manifested not on the portal of entry but on certain particular tissues or organs having a selective affinity, often at a distance and according to this specific action, the drugs are classified into different groups. Thus strychnine injected subcutaneously shows practically no action at the site of injection but this is manifested on distant places like the medulla and the spinal cord. Some of the drugs have specific action on the respiratory system. Others have special affinity for the heart, kidneys, digestive system or different glandular structures. Sometimes a drug acts

simultaneously on more than one system producing a more generalised *Systemic effect*.

THE GENERAL EFFECTS OF DRUG ACTION.—A drug may either *increase* or *diminish* the normal physiological function of a particular type of tissue and the result is either *stimulation* or *depression* of their functions : sometimes these actions may even alternate. This effect may be limited to a particular system or be more generalised. Sometimes a drug, which is stimulant in small doses, may act as a depressant when the dose is increased (as atropine) or on repeated administration even in the same dose for some time. Sometimes the function of one system may be augmented and that of the other, depressed. These actions are more manifested on specialised tissues such as the heart, nerves, muscles or the secretory glands.

In other cases, the action is one of *irritation*, manifested as alteration of cell nutrition and growth. This is more marked in comparatively less differentiated cells as epithelia and connective tissues.

Often this action is temporary so that as soon as the drug is either eliminated or oxidised, the normal function of the tissue is restored (*reversible action*) as with a volatile anæsthetic. But sometimes the tissue cells are so altered that such restoration is not possible (*irreversible action*) as following the application of a caustic.

In other cases again, the effect is *sensitization* so that some cells become hyper-receptive and respond to a weaker stimulus. Such a drug is strychnine. Or a few days after the administration of the first dose, the body as a whole gets into such a state that subsequently even a much smaller dose of it causes powerful local and constitutional effects (*allergy*). This is best seen when a foreign serum is given by injection and repeated after 10 days.

How a Drug Acts

A drug applied externally or taken internally, the action that follows may be one or more of the following.

(1) Some of the drugs act purely PHYSICALLY : these have neither direct nor indirect selective action on the tissues they come in contact with, except mechanically by their presence only. These, as applied *externally* on the skin, are substances like bland fixed oils, gums, mucilages and dusting powders. An example of one taken *internally* is liquid paraffin : this when taken by the mouth, does not undergo any change but only acts as a lubricant to the alimentary tract, facilitating the passage of its contents with greater ease without causing any effect on the surface epithelium.

Substances like carbon, infusorial earth or kaolin act by their power of *adsorption*. This is a process of physical fixation by which these substances are condensed or concentrated on

the surface of contact. Charcoal adsorbs gases and dyes : this and kaolin taken orally fix up bacterial and metabolic toxins in the alimentary canal. So *adsorption* is a process of separation of undesirable substances preventing their *absorption* or penetration through the epithelia of contact.

These thus act as *protectives, demulcents, emollients, adsorbants, astringents, irritants* (on the skin or mucous membranes) or as *sialogogues, flavouring, digestant, emetic or purgative* (on the alimentary canal).

(2) BY IONIZATION.—The mode of action of various inorganic salts is regulated by this process.

Inorganic acids, bases and salts are in the dry state electrically neutral but, when made into a watery solution, these dissolve into positive and negative ions. The base as Na, K and the like are positive and the acid as chloride or phosphate are negative ions. Thus—



The knowledge of these ions is very important because the action of an inorganic substance depends upon the relative importance of its ions, those of powerful properties prevailing upon those that are less active. Thus Potassium Chloride is more or less inert but Potassium Cyanide is a powerful poison. Here in either case, the action of the positive-ion potassium is the same but in one, the negative-ion chloride is inert and in the other, cyanide is a dangerous poison. Therefore the action of Potassium Cyanide is determined according to the action of the more powerful ion of the two, namely the negative ion, Cyanide.

But if this dissociation does not take place, the specific action of the ion is not manifested. In potassium ferrocyanide, the cyanide ion does not dissociate readily and so it is not poisonous.

The different ions have *special selective action* on different tissues. Thus Sodium-ion is more or less inert. Potassium, Calcium and Barium ions have special affinity for muscles ; Chlorine, Bromine and Iodine have for nerve-cells and Ammonia acts especially on the spinal cord and the medulla.

In addition to this selective activity of different ions, all soluble salts have another peculiarity based on their physical properties of penetration and this is called "*Salt action*". This depends on the rapidity with which a salt and the water keeping it in solution are capable of diffusing into the living cells placed in contact with.

If a solution of Sodium Chloride is separated from a similar solution of weaker strength by a permeable *dead* animal membrane, there is transfer of salt and fluid from one place to another till the two are equalised or made isotonic. This process is called *Osmosis*. The important point here is that all

salts pass through with equal readiness depending mainly on their molecular concentration.

An almost similar phenomenon with certain selective action takes place in the *living* body. Here the salt transfer depends, in addition to molecular concentration, on its power of penetrating the living cells.

The isotonic solution for the living tissue is one having the same salt-value as that of blood (these freeze at -0.52°). In order to investigate the osmotic tension of different solutions, red blood corpuscles are taken as the type of living cells. If these are placed in sodium chloride solution having the same density as of blood (sodium ion does not penetrate into the cells but remains in the extra cellular fluid) in isotonic or 0.9% solution, these will remain unchanged. But if placed in a fluid of less density (hypotonic), these slowly imbibe fluid, swell up and finally rupture. If, however, the fluid is of higher density (hypertonic), water being abstracted from these cells, these get crenated and shrunken. An easy absorption of fluid and salts from outside does not, however, take place with all salts.

K, Na, Li, Cl, Br, I are fairly quickly absorbed into the animal body and so also Ammonia and Urea (though the latter is not ionizable) even more readily. Ca is absorbed rather slowly and Mg., Sulphur and Phosphorus ions are even more sparingly. This selective affinity as shown by living tissues which allows some ions to penetrate more readily than others is *salt-action*. This is the essential factor regulating the pharmacological action of inorganic salts having no specific action of either of the ions.

If a salt in watery solution can enter into a living tissue, water keeping it in solution will also be readily absorbed but if the salt is not absorbable, water is not absorbed. Therefore if a solution of a non-absorbable salt in higher concentration than that of the body fluid, is kept in a chamber lined by living cells, an osmotic current starts which abstracts water from the tissue till a salt equilibrium is established. The fluid so collected will not be absorbed readily and cause only mechanical effects.

Therefore a non-absorbable or slightly absorbable salt solution is often given by the mouth which as passes through, increases the bulk of the intestinal contents, exerts pressure on the alimentary canal and acts as hydragogue purgative.

In the same way, salts that are excreted into the renal tubules, bronchial or sweat glands, by collecting fluid, act as diuretic, expectorant or diaphoretic.

(3) BY CHEMICAL ACTION.—A drug acts either (a) by chemically combining with some substances in the blood or in the tissues, (b) by its chemical affinity, fixes itself up to certain tissues in preference to others and its action is specially manifested on those tissues or (c) produce new active substances at the nerve ends which act.

An alkali when taken by the mouth, neutralises acids in the gastric contents and when absorbed into the blood adds to the alkaline reserve of the blood.

A volatile anæsthetic is absorbed into the blood unchanged and when it reaches the central nervous system, owing to its greater solubility in lipoid matter, it accumulates in the brain-lipoid in preference to other tissues and the specific action is manifested there.

In certain cases, it has been found that as a result of drug action, a particular chemical substance is liberated at the nerve endings which produces the effect. This is especially evident in drugs acting on the autonomic nervous system. Such a substance may be either acetyl choline or sympathin.

To find a possible explanation of the chemical action, the structural formulæ of several drugs have been studied. In some as in adrenaline and atropine, chemical compounds with allied formulæ have been found to have similar or even better therapeutic effect. But this is not true in many other cases and so the structural chemical formulæ of the drugs do not substantially explain the drug action in all cases.

(4) SPECIAL SELECTIVE ACTION.—A drug may have well-marked *selective action* on the whole or a particular part of the body even in minute doses but it is not easy to explain how it acts. It is not known if any chemical or physico-chemical changes take place. Most of the alkaloids act in this way.

This action in different parts of the body is often different not only in degree but also in kind. Thus chloroform acts more powerfully on the higher centres of the brain than on the lower vital centres in the medulla. Again, belladonna depresses certain peripheral nerve-endings but stimulates the brain.

(5) CHEMOTHERAPY.—This means combating systemic infection by "therapy" with "chemical agents" and is now occupying a prominent place, many newer highly effective agents being recently available. Certain *drugs*, as quinine in malaria, was known for a long time to have specific lethal action on the infective parasites of the disease without causing much injury to the host. Ehrlich suggested an explanation for this. Struck by the fact that certain vital dyes are able to stain a selected group of cells only, Ehrlich thought that such chemical substances might be produced as would unite with and destroy only the parasitic agents of disease without in any way injuring the cells of the body. This he called *chemotherapy* (high Parasitotropism and low Organotropism).

Several drugs and antibiotics have this sort of specific action. These are specially effective in many protozoal, spirochætal and bacterial diseases but not as much in most of the virus diseases. Anthelmintics may also be included in this group.

The more important of these are (a) for *bacterial infection*, sulphonamides, penicillin, streptomycin, aureomycin, chloramphenicol (chloromycetin) and terramycin: (b) for *protozoal*

infection, quinine and allied synthetic compounds (malaria); antimony preparations (leishmaniasis): emetine and arsenical and iodine compounds (amœbiasis): (c) for *spirochaetal infection*, mercury, bismuth and arsenical preparations and penicillin: (d) certain *virus infections*, aureomycin and chloromycetin.

In addition to the specific drug, the *co-operation of the tissue of the host* is an essential factor as an effect of similar intensity is not demonstrable in the laboratory *in vitro* by putting together the parasite and the drug even in a much greater concentration. Quinine or emetine will not as readily kill the specific parasites in an experimental condition outside the body except in a concentration that is considerably above the dose the host can tolerate.

The mechanism of parasitocidal action is uncertain. It may be as follows:

(i) A direct *chemical interaction* between the drug as administered or after its transformation in the body and some protoplasmic constituents of the parasite, resulting in death or injury to the latter by interference with its vital processes.

(ii) A *physical or physico chemical interaction* with the protoplasm of the parasites involving precipitation, changes in electrical charge etc., sufficient to destroy or injure the parasites.

(iii) The production of *new compounds* from the tissues as a result of action of the chemotherapeutic agent on tissue constituents which are the real active substances capable of chemical or physico-chemical interaction with the protoplasm of the parasites.

(iv) The production of *antibodies* by the release of antigenic substances from the dead parasites (Findlay).

The part that the cells of the *reticulo-endothelial system* plays in chemotherapy has been the subject of speculation. These cells have the power of engulfing foreign substances and take part in phagocytosis and other immunity response. Probably their activity is greater in bacterial than in protozoal infections and perhaps least in helminthic diseases. These may also act as store-house of the specific drugs, preventing rapid elimination and releasing them slowly at the site of the disease and may also be the avenue of formation of new active compounds from chemotherapeutic agents.

No drug has been found to be fully chemotherapeutic and every one of these has some toxic action on the host also though to a moderate extent. Therefore the minimal effective dose required for treatment to kill the infective organism, divided by the minimal lethal dose that will kill the host, $\frac{C}{T}$, should according to Ehrlich be $\frac{1}{3}$ or less. That is to say, for the drug to be useful therapeutically, this index must be fairly low, leaving an ample margin of safety. The CHEMOTHERAPEUTIC INDEX is $\frac{\text{Max. tolerated dose.}}{\text{Min. Curative dose.}}$ per kg. This should be never less than 3, preferably much higher.

Ehrlich at first thought that by a single massive dose it would be possible to kill all the parasites (*therapia magna sterilians*). But such a thing has not as yet been possible and several doses have to be given. It must, however, be remembered that too small doses given repeatedly may make the parasites resistant to further action of the drug. Again, this small quantity may be so readily destroyed or eliminated from the system that a parasitocidal concentration may never be reached.

RECENT CONCEPTIONS OF DRUG ACTION

Whatever may be the mode of administration of a drug and its distribution in the body, it acts only when it reaches certain specific tissue cells. If it accumulates inside the cells, it may reach the same or even higher concentration there than what is in the surrounding fluid medium. In other cases, the mechanism probably is prevention of its accumulation : penicillin is believed to act in this way by preventing the accumulation of glutamic acid in some of the cells. The action of the drug on the cell nucleus is more subtle and less obvious : this may be on the chromosomes and genes.

Highly potent drugs probably act on the tissue through certain *receptors* which are speculated to be localised on the surface of the cells or parts of an enzyme system : these fitting like keys in the locks. Chemical substances of a structure allied to the drug may show similar properties. On this assumption, efforts are made to synthesise newer drugs with allied chemical structure anticipating a similar pharmacological action.

Thus acetyl choline may occupy the receptors of a muscle or of a gland causing muscular contraction and glandular secretion. If an allied or even indifferent chemical substance has already been able to occupy the identical receptors, these actions fail. Two substances present in the medium surrounding the cells can thus compete with one another for the same receptors (*substrate competition*), one displacing the other.

Para-aminobenzoic acid and Sulphonamides have similar chemical constitution. The former is an essential metabolite for the growth and reproduction of bacteria : sulphonamides in therapeutic administration keep out this metabolite by substrate competition and stop multiplication of bacteria which are then easily destroyed by the natural defence of the body explaining the antibacterial action of sulphonamides.

The *enzymes* play an important part in the body activities and many drugs probably act through the enzymes. These functionate mainly as true catalyst and markedly accelerate the rate of chemical reaction. It is thought that any substance which in minute amount induces profound biological effects does so either by participating in or by specially affecting some enzyme system (Green, 1946).

Iron so important in cellular metabolism, is a component of catalase, peroxidases, cytochromes and lactic dehydrogenases. *Vitamins* are likely to be an intrinsic part of some enzyme system and are needed for the continual renewal of the enzyme which has only a short period of life (Green). Thus (a) vitamin A in the form of retinine acts in the visual purple of the eye. (b) Vitamin B₁ through carboxylase causes oxidation of pyruvic acid. (c) Of vitamin B₂, nicotinamide (antipellagra vitamin) is the essential constituent of cozymase, the co-enzyme of fermentation. (d) Pyridoxine or vitamin B₆ in the

form of its phosphoric ester is the co-enzyme of tyroxine decarboxylase.

Many *drugs* cause profound effect through enzyme system. (a) *Anæsthetics* probably act on the central nervous system reversibly by inhibiting a part of the respiratory enzyme system probably the flavoprotein component (Quastal, 1943). (b) Normally acetyl choline is inactivated by the enzyme cholinesterase. If substances like *physostigmine* are introduced, by substrate competition for cholinesterase, acetyl choline is spared which produces its specific action. *Ephedrine* also probably acts in the same way on the enzyme amine oxidase and protects the natural adrenaline from destruction. (c) Vitamin K or its synthetic analogue is the enzyme necessary for synthesis of prothrombin. *Dicoumarol* with a nearly similar chemical structure competes with vitamin K in the enzyme system and stops prothrombin formation. (d) It is suggested that the arsenicals and similar other metals produce their toxic effects by reacting with certain compounds in the pyruvate oxidase enzyme system (Peters, 1948). *Dimercaprol* (BAL) has been found an effective competitor to prevent such reaction and is used therapeutically for poisoning by these metals. (e) Penicillin is mostly excreted by the renal tubules. Carinamide (4-carboxyl phenyl-methane sulphonanilide) has action competing with it for the transport mechanism by blocking the specific enzyme responsible for the passage of penicillin through the tubules and consequently decreasing the excretion and increasing the penicillin blood level and its duration.

ISOTOPES.—The atom of a chemical consists of a nucleus of *proton* with positive electrical charge and *neutron* with no charge and surrounded by *electron* with negative charge: the atom thus is in neutral state. As neutral neutron can pass through an electrical field without deflection, it is capable of getting at and hitting a nucleus. The mass of proton and neutron is nearly the same but that of electron is about 1/2000th and much smaller. The atomic weight is according to its protons and neutrons but its atomic number (on which depends the chemical properties) depends on the number of electrons which again is the same as the number of protons in the nucleus. The atomic number varies from 1 to 92. Addition or removal of neutrons from an atom will not change its electrical charge. So two or more atoms of the same atomic number and consequently of identical chemical properties but with different weight may be possible and these are called **isotopes**.

In some cases the constitution of the atomic nucleus is unstable and it disintegrates emitting various types of rays and this atom is called *radioactive*. Of the rays emitted, alpha, beta and gamma, the last is more active and is the same as X-rays of very short wave length. The rate of disintegration varies at a wide limit. While radium disintegrates very slowly, carbon with an atomic weight of 11 (C^{11}) breaks up in some minutes.

Decay of half of the activity only is called half life of an element. Half life of radioactive isotopes recently used for pharmacological purpose are : of carbon (C^{11} and C^{14}), 205 minutes and 4.7×10^3 years : of phosphorus (P^{32}), 14.3 days : of sulphur (S^{35}), 87.1 days : of sodium (Na^{24}), 14.8 hours : of iodine (I^{130} , I^{131}), 12.6 hours and 8 days and of iron (Fe^{55} and Fe^{59}), 4 years and 47 days.

Uses.—(i) Radioactive isotopes may be used for pharmacological research. A substance or a drug whose passage through and the action in the body is to be investigated is marked or “tagged” with a homologous radioactive isotope which acts as a “tracer” and its presence in different part of the body can be detected by radiation that it emits. Thus by giving an intravenous injection of radio-active sodium, the state of peripheral circulation or the percentage of extra cellular sodium compared to the intracellular sodium may be determined. This data is of special value in a condition of shock as in a case of extensive burns. Diiodofluorescein containing radioactive iodine injected intravenously, may locate a brain tumour. Radio-active phosphorus may detect distribution of certain drugs in the tissue cells, especially in the cell nuclei.

(ii) Radioactive substances in atomic state administered *therapeutically*, cause identical effects as by the X-rays or radium. The effects are (a) *direct action* on an organic molecule : an atom forming a part of it when ionized, chemical changes appear in the molecule : these affect the structure of chromosome breaking this up and causing genetic effects. Radio-active phosphorus (P^{32}) has been used for this effect in diseases of the hæmopoietic and lymphatic systems. (b) Radiation may *ionize water* to produce hydrogen and hydroxyl radicals : the latter may act on and produce changes in other molecules. (c) This ionizing radiation may destroy *enzymes* causing far reaching effects. (d) Large protein *nucleus*, is also destroyed notably *viruses* : these include those viruses causing diseases in plants and in animals.

(iii) Atomic activity has been utilized for the *synthesis* of adrenaline, for formation of antibodies in the reticulo-endothelial system and for *assaying* deoxycortone. The other possibilities are rapidly developing.

MUTAGENIC SUBSTANCES.—Following the work with radiation on the cell nuclei, attempts have been made to produce mutation (change in character of the cells in growth) and multiplication by means of chemical substances. These chemicals appear to have a selective inhibitory action on particular types of cell growth probably by acting on the chromosomes. Thus oestrogens and androgens tend to inhibit the malignant growths involving the sex organs and the mammary glands. Nitrogen mustard in Hodgkin's disease, urethane in leukaemia and folic acid antagonists in certain malignant diseases and leukaemia

are other examples. Further investigations are in progress and valuable developments are anticipated.

Modification of Drug Action

The intensity and duration of drug action depend in general on the *dose*, mode of *administration*, the rate of its *absorption* and *accumulation* also *excretion*, *fixation* by an indifferent tissue and *detoxication* by such processes as oxidation, reduction or combination to form an inert product (Clark).

(1) **DOSE** : The quantity of the drug taken is most important. Bicarbonate of ammonia is expectorant in smaller but emetic in bigger doses. Atropine stimulates the central nervous system in smaller but paralyzes in bigger doses.

Arsenic, mercury, phenol, menthol and iodine are gastric irritants causing vomiting (*emetic*) but these in minute doses act as gastric sedative (*anti-emetic*) : digitalis slows the heart rate with therapeutic but quickens with toxic doses.

(2) Other important facts to be considered with this are, the influence of the *age*, *body-weight*, *sex*, *race*, *climatic condition*, *mentality* and *occupation* also any undue *idiosyncrasy* or *tolerance* : these affect the intensity of drug action.

(a) **AGE** : Children require a proportionately smaller dose (see p. 21). But they are over-susceptible to opium and to a less extent to strychnine, coal-tar antipyretics, alcohol, occasionally to mercury, arsenic and iodides. They are more tolerant to iron, belladonna, digitalis and calomel.

(b) **BODY-WEIGHT** : Other things being equal, the effect of a certain dose of the drug is inversely proportional to the body-weight, provided the latter is not due to undue obesity. So in some cases, dose per kilo gramme body weight has been fixed.

(c) **SEX** : Women during menstruation, lactation and pregnancy require careful consideration. Generally they require a smaller dose than men and especially so during these periods. During pregnancy, the drugs that act on the uterus or considerably lower the blood pressure, also irritant purgatives and diuretics (these tend to cause pelvic congestion) are contraindicated. During menstruation, purgatives increase the blood flow.

(d) **CLIMATIC CONDITION** : The climatic factor is important in some cases. Diuretics act more powerfully during winter than in summer. Alcohol is better tolerated in colder than in warmer climate.

(e) **IDIOSYNCRASY**. *—Some individuals are over-susceptible (occasionally resistant) to certain drugs, due to no obvious cause. This hypersensitiveness may be to a foreign protein (allergy) or to drugs like quinine, mercury, iodide of potassium, aspirin, arsphenamine, amidopyrine or to opium.

* Idiosyncrasy means peculiarity of temperament and susceptibility (G. *idios*, one's own and *syncrasis*, a mixing together).

(f) **MENTAL STATE** : If the patient is anticipating an effect, a small dose may be sufficient. A hypnotic at bed-time produces more powerful action than during the active hours of the day. On the other hand during the stage of excitement, a bigger dose of a sedative is necessary.

(g) **TOLERANCE**.—On the contrary, some individuals are resistant to the action of certain drugs. This may be *congenital*, i.e., existing from birth or acquired by frequent intake of smaller doses, as of opium, alcohol, tobacco or of arsenic.

This tolerance may be somewhat localised being more marked in certain parts of the body. Thus for action as a cerebral sedative an increasing dose of opium is necessary but not for action on the intestine to cause constipation.

Further prolonged use of one drug increases tolerance for another in the same group as an alcoholic is more resistant to ether and chloroform.

This habituation may be due to diminished *absorption*, increased *elimination*, increased *destruction* of the drug in the system, increased *functional tolerance* or formation of *antibodies* in the system. “Drug habit” or taking certain intoxicating drugs in increasing doses to cause pleasurable sensation (*euphoria*) is a serious problem with some individuals.

The important of these in India are opium and its alkaloids especially diamorphine and morphine, Indian hemp, alcohol, cocaine and occasionally chloral hydrate and barbiturates.

An infective organism may also be “drug resistant” if treated with many frequent small doses below the therapeutic level. This is very important with streptomycin.

(3) **RAPIDITY OF ABSORPTION AND ELIMINATION**.—Drugs administered *orally* on empty stomach show more rapid action than when given after food : even more rapid action follows an *intravenous injection* : rapid *destruction* in the liver and quick *elimination* by the kidneys cause less sustained effect.

(4) **CUMULATIVE EFFECT**.—Certain drugs are slowly or imperfectly eliminated and so with repeated administration a portion accumulates in the system. The same effect may happen from sudden increased absorption, diminished elimination and also from disturbances with the mechanism of detoxication by the liver, kidneys and other tissues. This accumulated amount may after some time give rise to sudden symptoms of over-action and even when further administration is stopped, this action may continue for some time. The best example is digitalis and to some extent, mercury, arsenic, lead, bromides, iodides, strychnine and emetine.

(5) **EFFECT OF COMBINATION**.—This may be either an increase or diminution of the effects of the several drugs combined or appearance of an entirely new action due to the formation of some new compounds.

(a) *Synergists*.—Sometimes two or more drugs of similar actions are combined to produce a more certain and powerful action, as for instance, several purgatives are often combined. For the same reason, bismuth or mercury is given along with

arsenic for the treatment of syphilis. The result may be either *summation* of effects of several drugs prescribed or more *intensification* though rarely may be even slight lowering of the total effects.

(b) *Antagonists*.—Often several drugs having opposite action are combined, one as a corrective of the other, in order to counteract certain disadvantageous effect. Atropine is combined with morphine to counteract the depressant action of the latter on the respiratory centre. A sedative as chloroform by inhalation or a barbiturate by injection is used to control the convulsions of strychnine poisoning.

(6) THE PATHOLOGICAL CONDITION OF THE TISSUES.—Sometimes drug action is better manifested in disease than in health as antipyretics act more powerfully when the temperature is high. In other cases, the response may be less ; sedatives are required in bigger doses in a state of nervous excitement or pain. Adrenaline is an effective bronchodilator in asthma but not in health.

The pH of the tissue is important in some cases. Emetine acts better on the *E. histolytica* in the intestine in an alkaline tide whereas the mercurial diuretics act more powerfully in a condition of slight acidosis.

(7) THE PECULIARITIES OF CERTAIN DRUGS are also important. Although usually rapid introduction as by intravenous injection of a drug may cause immediate toxic effects, this may sometimes be slow and cumulative as with arsenobenzols. In another case, a bigger single dose may be comparatively harmless but several smaller repeated doses may be toxic as with lead.

(8) THE TIME AND THE METHOD OF ADMINISTRATION.—These are very important and discussed in detail. The body refreshed after night's rest is more resistant to drug action in the morning than in the evening. This is especially so with narcotic drugs. Further, more rapidly the drug enters into the circulation, quicker and more powerful is the action ; and less destruction or elimination of it, more sustained is the effect. Drugs rapidly eliminated as sulphonamides or penicillin require frequent administration to keep up the effect.

THE METHODS OF DRUG ADMINISTRATION

(i) BY THE MOUTH : The most convenient and popular method of administering any drug is by the mouth (*per os*). It has the advantage of simplicity and is also most convenient for self-administration.

The drug or drugs are made into gargles, paints, pastilles, sprays, mixtures, pills, capsules or powders for the convenience of either dispensing or administration. These are prescribed for *local*, *systemic* or *reflex effect*. Some drugs given by mouth causes local effects only but if given by injection, different

systemic effects : the examples are magnesium sulphate, emetine and antimony preparations.

Linguetes—Drugs as tablets of penicillin, a gonadotropin, desoxycorticosterone, isopropyl epinephrine preparations and of trinitrin are sometimes kept in the mouth or under the tongue for slow local and systemic actions.

Administration by the mouth is especially indicated (a) when *local action* on the alimentary canal is desired, for the relief of throat affections or for causing or stopping emesis or purgation.

(b) This is when *after absorption* the maximum concentration of the drug is required in the portal circulation, as of quinine.

The absorption of the drug is rather slow sometimes uncertain but is sustained and when rapid action is desired, the drug is given on empty stomach. If, on the other hand, it is desired to have more sustained absorption or when from the nature of the drug it is thought to be too irritant for the empty stomach, as preparations of iron or arsenic, it is given well diluted or soon after a meal.

Intestine is the usual site of absorption, *stomach* mainly transmitting. Hence healthy or diseased condition of the stomach and the intestine and the *physical property* of the drug, in solution or otherwise, are factors which regulate absorption. Usually drugs in solution especially in alcohol are readily absorbed. Presence of gums and resins also of other colloids in general delay. Volatility and penetrability of a drug (salt action) are also important factors. Drugs with disagreeable taste are made into tablets or pills or put inside capsules or cachets or flavoured with various sweetening agents. To avoid local action on the stomach, pills are keratin-coated. Drugs absorbed from the stomach and the intestines are first carried to the liver before reaching the heart and the general circulation and the condition and efficiency of the liver are often determining factors of the effects produced in the system.

(c) *Reflex effects* are produced from the mouth on the gastric secretion if the drug has a sharp taste as by vegetable bitters. The same may happen from the stomach on the cardio-acceleratory mechanism causing forcible heart action as by moderately diluted alcohol.

(ii) RECTAL ADMINISTRATION.—Here the object is either to distend the rectum with a fairly large quantity of fluid, often combined with one having slight irritant action, to help evacuation (this is called an ENEMA) or a smaller quantity of isotonic fluid is given with minimal distension so that there may be the least local irritation and the fluid is retained and absorbed. Water, many salts, alcohol, several hypnotics, basal anæsthetics and glucose solution are absorbed from the small intestine and also absorbed from the colon but more slowly.

(iii) INHALATION.—Volatile drugs like chloroform, ether, oxygen and carbon dioxide are given by inhalation in order to produce a *systemic effect*, the drug being brought into the lungs with the inspired air and absorbed into the general circulation therefrom. An irritant as inhalation of ammonia salts causes *reflex effect* on the circulation and respiration in a case of syncope. Many aromatics and volatile oils are given in the same way for *local effects* on the upper respiratory passages.

Mercurial vapours (by fumigation) are not nowadays used by inhalation.

Aerosol therapy.—With a fine nebuliser driven by oxygen jet or air pump, drugs or antibiotics especially penicillin have been sprayed into the tracheo-bronchial tree.

(a) Penicillin, 2500 to 4000 units, has been sprayed every three hours.

(b) In condition of much mucosal swelling, 1 in 100 adrenaline chloride solution 0.5 to 1 c.c. is sprayed.

(c) Pitressin is also similarly sprayed in diabetes insipidus.

(iv) INUNCTION.—Some drugs are mixed with a fatty basis, less commonly, alcohol or ether and are rubbed into the skin for *local effect* on the place or for *systematic effect* after absorption. Most of the liniments belong to the former and ointments of mercury, stilboestrol and occasionally cod-liver oil to the latter group.

(v) Besides these, lotions as wash, gargle, spray, douche or drops : powders for dusting and insufflation or blowing into the nose : plasters, blisters, caustics, ointment creams, suppositories and pessaries are used for producing various *local effects* on the skin and the mucous membranes.

(vi) SUBCUTANEOUS METHOD.—This route is chosen either for rapid absorption of a drug in solution (preferably in water) or for a drug which, on account of its local action on the stomach, cannot be given by the mouth, as emetine. The solution should be sterile, isotonic and almost nonirritant.

The methods chosen are (a) *injection*, subcutaneous and intradermal, (b) *skin scarification* and (c) *implantation* of sterile tablets into the subcutaneous tissue.

The absorption is facilitated by a recently introduced spreading factor, *Hyaluronidase*, a mucolytic enzyme. For an electrolytic saline solution as normal saline, 1 μ g. may be sufficient per 10 ml. or more given subcutaneously : added to penicillin solution, a higher blood level is quickly reached and this injected into a diseased tissue, rapid penetration takes place : used in infiltration anaesthesia, a wider area is anaesthetised.

The favourite sites for subcutaneous injection are loose tissues of the upper arm or thigh and for a large quantity of fluid, (*hypodermoclysis*), inner aspect of the axilla, submammary space, flank or the inner side of the thigh.

Intradermal injection.—Sometimes a vaccine is injected into the skin just below the epidermis with a small hypodermic syringe having a fine sharp needle. The fluid forms a white wheal. Better immunity response is said to be obtained by this. This method is also utilized for many diagnostic tests for specific sensitization and for the treatment of leprosy with hydnocarpus oil.

Vaccine lymph is applied on the skin after superficial *skin scarification*. Sterile oestrogen or desoxycortone tablets are occasionally *implanted* into the subcutaneous tissue for prolonged action.

(vii) INTRAMUSCULAR METHOD.—Here the drug is either too irritant to be given subcutaneously, as quinine : or a more rapid absorption is necessary than is possible from the subcutaneous tissue, as of a specific antiscrum.

A sterile isotonic *watery* solution is readily absorbed and so is more suitable. Sometimes an insoluble substance in *oily* or watery *colloidal* suspension is also administered in this way to form a depot of it in muscles ensuring slow but sustained absorption for a long time.

Bismuth or mercurial creams also gonadotropic hormones, desoxycortone, penicillin in oil and wax or in aqueous suspension and zinc protamine insulin are the usual preparations.

Disadvantages of these two methods are local pain, sepsis and sometimes lumping at the site of injection. Rarely a superficial vein may be punctured drug entering the blood directly which may be harmful. Injections given near a nerve may cause toxic neuritis.

Intracardiac injection.—Sometimes in sudden syncope when the heart itself is all right, drugs like adrenaline chloride solution is injected directly into the heart muscles, sometimes with favourable results.

(viii) INTRAVENOUS METHOD.—Here the drug is thrown straight into the general circulation either because (a) the quantity required to be given is too large to go under the skin, (as a saline solution), (b) a more rapid concentration of the drug in the blood is desired than is possible with any of the previous methods, (as quinine in pernicious malaria or a specific antiserum) also in certain sudden emergencies or (c) the drug is too irritant to be given either subcutaneously or intramuscularly (as an inorganic antimony preparation).

The drug should be in sterile watery solution, nearly isotonic, at blood heat, of pH approaching that of blood, should not contain foreign protein, be of convenient volume, freshly prepared and introduced slowly.

The neat and correct puncture of the vein and not too frequently using the same vein (which may cause obliterating phlebitis) are essential.

The intravenous method is required for *therapeutic drug administration*, (as for arsenobenzols, antimony preparations, strophanthin, leptazol, antitoxic sera, sulphonamides or penicillin), *general anaesthesia* (usually with a barbiturate), altering the *blood constituents* (as with saline, glucose, blood plasma, sodium bicarbonate and calcium preparations) and for *diagnostic tests* (with indigo carmine, abrodil or uroselectan).

But the advantage of rapid introduction of the drug has the disadvantage of its rapid elimination. So the action is likely to be less sustained.

The above three are also called *parenteral methods* of drug administration.

(ix) INTRATHECAL METHOD.—Sometimes a drug is injected into the thecal space following lumbar puncture for its more intensive action on the cerebro-spinal system as stovaine, given for spinal anaesthesia and anti-meningococcus serum for cerebro-spinal fever.

In suitable cases, *Cisternal* and *Intraventricular injections* are also given.

(x) **IONIC MEDICATION** (*Cataphoresis, Iontophoresis*).—Here a soluble ionizable salt is dissociated by means of a galvanic current and a particular ion of it is driven into the subcutaneous tissue for more active and concentrated local effect than is otherwise possible.

To have the action of the metal or the basic radicle, a lint soaked in a solution of the salt is applied on the diseased area and on it is put the positive (anode) and if of the acidie radicle, the negative pole (kathode). The indifferent pole is applied on the skin over the spine through a lint soaked in normal saline. The positive pole repels the positive and the negative pole, the negative ion. The repelled ion enters into the subcutaneous tissue. But in reality not enough gets in (and that also not beyond the superficial tissues) to have dependable therapeutic effects.

As for example, potassium iodide or sodium salicylate in concentrated solution is applied on a thin piece of lint over a place in chronic inflammation and the negative pole of an electric circuit is attached to it. The positive pole is applied on the spine behind or to the skin nearby. The negative ion iodide or salicylate is dissociated and gets into the subcutaneous tissues being repelled by the negative pole.

More recently for the treatment of peripheral vascular disease, chronic ulcers and arthritis, acetyl-beta-methyl choline in 0.25 to 1% solution wetting a cotton pad is placed under the positive electrode of a galvanic machine and applied on the affected area or near to it.

The other electrode on a moist pad is applied on the back. A current of 20 to 50 milliamperes is employed for 20 to 30 minutes twice or thrice weekly.

Sometimes it may be necessary to combine these various methods, one drug being given in one way and the other by a different route. These act either as synergists or one correcting certain disadvantageous action of the other.

Doses of Drugs

The Pharmacopœia has prescribed doses for various medicinal preparations, directing the minimal and the maximal limits. The former is the minimal quantity which shows any physiological action and the latter is the indication of the safe limit that can be tolerated under usual conditions without showing toxic symptoms. The individual susceptibilities which sometimes exist and usually cannot be anticipated in advance are considerations: *idiosyncrasy*. These vary so greatly in different people, some of them being oversusceptible and less commonly, others being more tolerant, that such fixing up of the upper and the lower limits of the doses becomes necessary. But under special circumstances, the prescriber may need to overstep the maximum dose limit in which case he must signify his intention by initialing the overdose.

Full or adult dose is given between the ages of 20 and 60 years and after this, it should be slightly reduced. For

children under 12, the dose is usually calculated in the following way,—

YOUNG'S RULE.—Add 12 to the age of the child and divide the age by the number so obtained. Therefore for a child of 5 years, the dose should be $5 \div (12 + 5) = 5/17$ th of the adult dose.

DILLING'S FORMULA.—Multiply the adult dose by the fraction obtained by dividing the age by 20. This is convenient in calculating dose of metric measure.

COWLING'S FORMULA.—Multiply the adult dose by the fraction obtained by dividing the age next birth day by 24.

CLARK'S RULE is to divide the weight of the child by 150 and the result is the fraction of the adult dose.

But in certain cases this rule is not followed especially in the administration of an *antitoxin* where the degree of toxæmia is the main determining factor and in the *glandular* or *hormonic products* where the dose is according to the degree of deficiency.

Susceptibility of children.—It is worth remembering that children are very sensitive to opium and also in some extent to strychnine, and therefore some caution is necessary in fixing up the dose if these are to be prescribed.

Sometimes a variable drug action is not due to any individual susceptibility but to uncertain composition of the drug. Thus a preparation may not contain the full amount of its active principles. This may be due to the crude sample being obtained from an indifferent source or to its deterioration from prolonged (or careless) storage. Therefore in the case of drugs having powerful active principles, it becomes necessary to fix up the dose of a preparation not exactly according to its quantity of the crude substance used but according to its active principle contents. This is called *Standardisation*.

This standardisation is mostly done on chemical basis (*Chemical Assay*) according to the proportion of its most powerful chemical constituents as of morphine in Opium or of strychnine in Nux Vomica. But in the case of a few like Digitalis, it cannot be done in this way owing to the unstable nature of its active principles which are not easy to isolate in stable form for chemical estimation. Several animal products as Adrenaline, Posterior Pituitary Extract and Insulin also come under this group, being unsuitable for the usual chemical standardisation.

These are consequently standardised according to their physiological action, by observing either the minimal fatal dose* or some change in the normal function of certain isolated organs or tissues. Thus while the proportion of the active principles in a preparation of Opium or of Nux Vomica goes by the

* As individual sensitivity of drugs may vary, a dose that will kill 50% of the animals experimented on has been taken as the average lethal dose, M.L.D.

percentage of its morphine or strychnine content, in case of Digitalis, it is in terms of cat or frog-units according to the quantity required to stop the heart-action of a cat or a frog of a certain body-weight. This method of standardisation is called *Biological Assay*.

BIOLOGICAL ASSAY

The British Pharmacopœia (1948) directs that following should be standardised biologically :

(1) **DIPHTHERIA ANTITOXIN**.—The potency is determined by comparing the dose of it necessary to protect guinea-pig weighing 250 to 270 grammes against the effect of a fixed dose of diphtheria toxin, with the dose of a standard preparation of diphtheria antitoxin necessary to give the same protection.

L† dose of toxin is that amount which mixed with one unit of standard antitoxin injected will cause death of guinea-pig within 4 days. With the same standard toxin, different volumes of the serum to be tested are mixed and injected subcutaneously into guinea-pigs. The amount which will cause death after 4 days, contains one unit.

(2) **GAS-GANGRENE ANTITOXIN** (Perfringens, Œdematiens or Septicum).—The potency is determined by comparing the dose of it necessary to protect mice or other suitable animals against the lethal effect of a measured quantity of specific gas-gangrene toxin with the dose of the standard preparation of same type of gas-gangrene antitoxin necessary to give the same protection.

(3) **TETANUS ANTITOXIN**.—The potency is determined by comparing the dose of it necessary to protect guinea-pigs or mice against the lethal effect of a fixed dose of tetanus toxin with the dose of a standard preparation of tetanus antitoxin necessary to give the same protection.

L† dose of the toxin is that which mixed with 0.2 unit of antitoxin causes death of a guinea pig or mice in 4 days. So if the volume of antitoxin mixed with L† toxin injected into the animal, keeps it alive for 4 days, has 0.2 units.

(4) **OLD TUBERCULIN**.—The potency is determined by comparing the dose of it given subcutaneously necessary to produce its specific inflammatory reaction in guinea-pigs or other animals infected with the tubercle bacillus, with the dose of the standard preparation necessary to give the same effect.

(5) **PREPARED DIGITALIS : TINCTURE OF DIGITALIS**.—The standardisation is done by administration of digitalis by injection on batches of frogs or cats and the lethal dose of it as compared with the standard digitalis preparation, determines the activity.

A suitable solution of the extract of the standard preparation is injected into the ventral lymph sac of a batch of frogs weighing between 15 to 30 grammes. The same is done to another batch with the sample to be tested. The number of frogs dead next day is made out and from this the potency is calculated (50% death is potency of 100), or the solutions are slowly injected intravenously to anæsthetised cats or guineapigs till the heart action is topped (lethal dose). The potency is determined by dividing the average

Standards for Biological Assay at the National Institute for Medical Research

| Standard Preparation | Nature of the standard | Unit in mg. | Relation to international unit | Form in which supplied |
|-----------------------------------|--|-------------|--|--|
| Antitox. | Dried antitoxin | 0.1279 | Same | As standard sol. |
| Diphtherie | | | | 10 units/ml. |
| ... Tetanic | As above | 0.1770 | Same | As above. |
| ... Gasgangrene | As above | 0.1135 | Same | As sol. 20 units/ml. |
| (œdemat) | | | | |
| ... Welchie | As above | 0.1132 | Same | As above. |
| (perfrigans) | | | | |
| ... Septicæm | As above | 0.0974 | Same | As sol. 50 units/ml. |
| ... Staphylococ. | As above | 0.23% | Same | As sol. 20 units/ml. |
| Digitalis | Dry powder leaves of <i>digitalis purpurea</i> | 80.0 | Same | Approx. 3 g. in sealed ampoule. |
| Gonadotrophin chorionic | Urine of pregnancy dried and diluted with lactose | 0.1 | Same | Twentyfive 10 mg. tablets in sealed ampoule. |
| Gonadotrophin serum | Serum of pregnant mares dried and diluted with lactose | 0.25 | Same | Ten 25 mg. tablets in sealed ampoule. |
| Heparin | Dried sodium salt | 0.0077 | Same | Approx. 50 mg. in sealed ampoule. |
| Insulin | Dry crystalline insulin hydrochloride | 0.0455 | Same | Approx. 20 mg. in sealed ampoule. |
| Penicillin | Dry crystalline sodium salt of penicillin II or G | 0.00065 | Assayed in terms of international standard | Approx. 30 mg. in sealed ampoule. |
| Pituitary powder (posterior lobe) | Dry acetone ext. of post. pituitary | 0.5 | Same | As above. |
| Neoarsphenamine | Dried sample | — | Same | Approx. 0.3 g. in sealed ampoule. |
| Sulpharsphenamine | Same | — | Same | As above. |
| Ouabain | Crystalline ouabain | — | Same | Approx. 100 mg. in sealed ampoule. |
| Strophanthus (tincture) | Tincture | — | Assayed in terms of standard ouabain | As tincture of stated potency. |
| Tuberculin, old | Glycerin sol. of old tuberculin | — | Same | As standardised glycerin sol. |
| Vitamin A | Dry betacarotene | 0.0006 | Same | As standard sol. of 200 units/g. |
| Vitamin D | Irradiated ergosterol in olive oil | 1.0 | Same | As standard sol. of 1000 units/g. |

lethal dose of the standard preparation by the lethal dose of the sample under test.

(6) TINCTURE OF STROPHANTHUS.—This is done in the same way as for tincture of Digitalis.

(7) HEPARIN.—The potency is determined by comparing the concentration of it necessary to prevent the clotting of shed blood or of a fluid that takes part in clotting of shed blood, with the concentration of the standard preparation necessary to give the same effect.

(8) INSULIN.—The potency of a sample is estimated by comparing hypoglycæmia caused by it with that by the standard preparation of insulin under the condition of a suitable method of assay.

Twelve healthy rabbits, weighing about 2000 grammes and starving for about 18 hours are taken and divided into 2 batches. The first batch is divided into 2 groups: one gets 2 units and the other 1 unit of standard insulin subcutaneously and the second batch is also divided into 2 and gets the probable 2 and 1 unit of the insulin to be tested. The blood sugar of each is estimated hourly for 5 hours and the average reduction noted. Four days after, the test is repeated but the batch which received the standard sample, now receives the test sample and the blood sugar is estimated in the same way.

The sum of the numbers for the percentage of blood sugar reduction for two days by the standard sample divided by the same of the test sample and the result multiplied by 100 gives the percentage strength of the test sample in terms of the standard preparation.

The retardation effect of hypoglycæmia produced by *protamine zinc insulin* is compared with hypoglycæmia caused by standard insulin by rabbit assay.

The preparation being tested is injected without previous dilution. The standard solution is made up to possess the same activity as the preparation on test is expected to possess in equal volumes. Blood should be taken every hour for test. Blood sugar with the standard insulin should reach the initial level in about 5 hours.

The average blood sugar curves for the standard and the test preparations should be plotted on the same diagram. At a time when the average blood sugar percentage of the rabbits receiving the standard has just reached the initial level, that of the rabbits receiving zinc protamine insulin should not be more than 80% of initial level.

(9) PENICILLIN.—The potency of a sample of penicillin is determined by comparing the dose which inhibits the growth of a sensitive strain of staphylococcus with the dose of the standard preparation of penicillin which produces the same inhibition.

Standard preparation is the sodium salt of pure penicillin II or G. The unit is contained in 0.00065 mg. of the standard.

Petri dishes with agar medium are inoculated with a suitable culture of staphylococcus; solutions of standard preparation as 0.5 to 2 units per mil. and solutions of the sample to be tested are filled into cylinders 10 mm. high and 5 mm. in internal diameter, made of glass. These are put on the plates. These plates are incubated at 37° for 16 to 24 hours and the diameter of the inhibition zones are accurately measured; from this the potency of the sample is estimated.

(10) NEOARSPHENAMINE.—For absence of undue *toxicity* : the average lethal dose of the standard preparation is 7.2 milligrams for a mouse weighing 10 to 15 grammes.

Of the 2% solution, 0.3 ml. is given intravenously to 10 mice : if not more than 2 die within 3 days, the sample has passed the test. If more, another 10 mice are next injected. If the total death in the two batches is not more than 8, the sample has passed the test.

For therapeutic potency : A mouse artificially infected with trypanosomes is injected intravenously with 0.03 milligram of the drug per gramme of body weight of the animal. Trypanosomes should disappear from the peripheral blood in 48 hours.

(11) SULPHARSPHENAMINE.—It is tested in the same way but the drug is injected subcutaneously. Further, a 10% solution in a dose of 0.35 mg. per g. of body weight should not cause local œdema or necrosis.

(12) SERUM GONADOTROPHIN.—The activity of a preparation is determined by comparing its gonadotrophic activity with that of the standard preparation.

The weight of the ovaries of the immature female rat can be increased by the above from about 10 mg. to a maximum of about 220 mg. This increase is the basis of the assay.

(13) CHORIONIC GONADOTROPHIN.—The activity of a preparation is determined by comparing its gonadotrophic activity with that of the standard preparation.

The weight of the ovaries may be increased from 10 mg. to 40 mg. or more.

(14) POSTERIOR LOBE OF PITUITARY EXTRACT.—It has 3 principles, *oxytocic*, *antidiuretic* and *pressor*. These are tested on various animals.

(a) The *oxytocic* potency is determined by comparing the contraction of the uterus of a female guinea-pig, weighing 170 to 270 grammes, as soon as weaned, suspended in an oxygenated special saline water bath at 37° to which a suitable dose of standard solution usually 0.05 to 0.1 unit is added, with the contractions caused by the sample tested, in similar condition.

(b) *Antidiuretic activity* is tested with male rats, weighing between 120 to 240 g. kept without food overnight., 5 ml. of warm water per 100 g. of body weight is given by stomach tube. To one group 0.006 unit of the standard per 100 g. of body weight is injected and to the other group, the test sample in probable equivalent dose. Urine is collected for 3 to 4 hours. After 24 hours, the group that received the standard preparation now receives the sample to be tested. From the results, the mean time for the excretion of half the volume of urine in two cases are compared.

(c) *Pressor effect* is assayed in anæsthetised healthy cats by intravenous injection of the standard preparation and the test sample.

(15) VITAMINS :

Vitamin A is standardised by comparing its (a) activity in increasing the weight in rats which have ceased to grow on a deficient diet or (b) by spectrophotometric method, with the standard kept in the National Institute of Medical Research, Hamstead, London.

Aneurine hydrochloride is assayed by comparing either by visual method or by photoelectric method, the fluorescence produced by the reaction with potassium ferricyanide under standard condition with the same produced by the standard.

Vitamin D is standardised by comparing its protective and curative efficiency in rickets with the standard preparation by a suitable method and is expressed in units per gramme.

(a) *Prophylactic assay*.—About 20 young rats each weighing 40 to 50 grammes in two groups are fed on rachitogenic diets for 4 to 5 weeks. To one group is given in addition, 0.025 to 0.1 unit of the standard preparation of vitamin D and to the other group, the preparation to be tested. At the end of the period, the rats are killed and the bone ash of the two groups are determined. The average percentage of bone ash of the rat fed on the preparation tested, against the same of the rat fed on the standard, shows the strength of the preparation.

(b) *Curative assay*.—Rats are divided in the above way into two groups and fed on rachitogenic diet for 3 weeks and the degree of rickets caused is determined by X-ray examination. One group is now given a daily dose of 2 to 8 unit of the standard preparation and the other group, the preparation to be tested for a period of 10 to 14 days. The rats are now killed and the extent to which rickets have been cured is estimated. The strength of the preparation tested depends on the extent of cure as compared with the cure by the standard.

PHARMACY

Pharmacy is the art of preparing, compounding and dispensing of drugs. This is not nowadays strictly the work of a medical practitioner and has been taken up by the manufacturing and dispensing chemists.

The *inorganic* Materia Medica consists of several metals, metalloids, mineral acids, alkalies and their salts. Some of the salts are neutral in reaction and the others are either acid or alkaline. These are obtained naturally or are synthesised.

The *organic* preparations include various plant and animal principles and are very varied in their chemical nature. Some of these have been prepared synthetically also and with the progress of chemical research, their number is increasing.

In addition, there is a large group of **hydrocarbons**. These are specially prepared from various plant and mineral products.

(i) The open chain or *aliphatic* hydrocarbons. This group includes paraffins, alcohols, aldehydes, acids, ether, esters (compounds of ether and organic acids), sulpho-derivatives, carbonic acid derivatives and carbohydrates.

(ii) The closed chain or *benzene* hydrocarbons.—This group includes various benzene derivatives, phenol derivatives, aromatic alcohols and other aromatics.

(iii) The irregular rings.—These include naphthalene and anthracene hydrocarbons.

THE PLANT AND ANIMAL PRINCIPLES

These may be grouped as follows :

- (i) Proteins, vegetable, animal or bacterial.
- (ii) Lipoids, as fats, oils, cholesterol and waxes.
- (iii) Carbohydrates, as starch, sugars, dextrin, gums, cellulose, glycogen and pectins.
- (iv) Organic acids as benzoic, cinnamic, citric, malic, oxalic and tartaric acids, combined with alkaloids or bases as calcium, potassium or sodium.
- (v) Alkaloids.
- (vi) Glycosides including saponins and sapotoxins.
- (vii) Volatile or essential oils.
- (viii) Steroptenes, as camphor, menthol and thymol.
- (ix) Resins, oleoresins, gumresins and balsams.
- (x) Miscellaneous substances as Enzymes (animal and vegetable), Bitter principles and Colouring matter as chlorophyll, carotene and xanthophyll.

Alkaloids.—These are amides or amines, (substituted ammonia compounds), being alkaline in reaction.

In Nature, these exist in many plants : *in larger proportion* in the *seeds* and *roots* in combination with various vegetable acids. Like alkalies, they

readily combine with acids to form salts which are soluble in water and the solution is intensely bitter. But free alkaloids are comparatively insoluble in water and are soluble in acids, solvent ether, chloroform and to some extent in alcohol and oils. The name of all alkaloids ends in *-ine* and except atropine, caffeine, cocaine, codeine, ephedrine, ergometrine and totaquine, none of these by themselves are official. Their various salts are, however, official. Many of these are chemically related to *pyridine* (as nicotine), *quinoline* (as quinine), *isoquinoline* (as papaverine), *phenanthrene* (as morphine and codeine) and *pyrrolidine* (as atropine and cocaine). Many of these may be synthetically prepared.

Except coniine, lobeline, nicotine, pilocarpine and sparteine, which are liquid, all of these are solid and are colourless and crystalline.

The common alkaloidal precipitant used for chemical test is Mayer's reagent.*

Balsams.—These are the combinations of oleoresins, with aromatic acids as benzoic or cinnamic acid or both obtained as viscid exudates from the trunk of certain plants.

Benzoin, storax and balsams of Peru and Tolu are in B.P.

Bitters and neutral principles are bodies of ill-defined chemical character.

These are either amorphous, resinous or crystalline. Aloin, cantharidin, cubebin, santonin, calumbamin, quassin, and aristolochin are examples. These end in *-in*.

Enzymes or ferments cause chemical changes without they themselves getting incorporated in the change. These are substances like pepsin, pancreatin and lactase.

Glycosides—These are colourless crystalline bodies, containing carbon, hydrogen and oxygen, occasionally in addition, nitrogen and rarely sulphur: neutral in reaction, and are readily split up (hydrolysed) by ferments and dilute acids into one or more of the substances like glucose (called *glucosides*) and sometimes other sugars, and also *aglucones* or *genins*. Many of these are closely related to one another containing 23 carbon atoms but the arrangement of the oxygen atoms is different. Several of these are active poisons but others are somewhat inert.

These differ in their solubility in water and alcohol and only a few are soluble in solvent ether. The important glycosides are colocynthin, digitoxin, gitoxin, gitalin, gentio-picrin, glycyrrhizin, jalapin, salicin, saponin, scillareu, senegin and strophanthin.

Gums, somewhat related to cellulose and starch, are exudation from the stems of plants. These dissolve in or swell up with water to form viscid substances. These are of three kinds :

- (i) Soluble gum.—Arabin, acacia, Indian gum.
- (ii) Partly soluble gum.—Bassorin, tragacanth.
- (iii) Insoluble gum or cerasin.

Pectin allied to gums, forms vegetable jelly.

* *Mayer's reagent*.—Dissolve 1.35 grms. of mercuric chloride in 60 mls. of water : dissolve 5 grms. of pot. iod. in 20 ml. of water. Mix the two and add sufficient water to make 100 ml.

Gum-resins.—Some plant-exudates are mixtures of gum and resin and often of some volatile oils as asafoetida and myrrh. When mixed with water, the gum being dissolved, the resin is kept in suspension.

Two well-known are ammoniacum and asafetida.

Oils.—These are of two kinds : **FIXED OILS** and **FATS** and **VOLATILE OILS**.

FIXED OILS are (i) prepared by expressing these from various fruits and seeds and also from animal tissues : (ii) at ordinary temperature, these are liquid, more or less yellow in colour and float in water : (iii) insoluble in water, slightly soluble in alcohol and freely so in benzol, carbon disulphide, chloroform, solvent ether and in turpentine oil : (iv) leave a greasy mark on a paper and cannot be separated by distillation : (v) can be saponified easily and emulsified : taken internally, are completely oxidized in the body and excreted as CO_2 and H_2O : (vi) may become rancid on exposure to air and heat.

Chemically, these are the combination of fatty acids (oleic, palmitic and stearic), and glycerin. These when acted on by caustic alkalies and metallic oxides, form soaps and glycerin.

There are 10 fixed oils in B.P. ; almond, castor, cod-liver, cotton seed, ground nut, halibut-liver, hydnocarpus, linseed, olive and sesame oils.

Ethyl esters of hydnocarpus oil and iodised oil may be added.

FATS.—These are fixed oils and are solid at ordinary temperature on account of containing more palmitin and stearin.

These are, oil of theobroma (tends to liquefy in hot weather), prepared lard, suet, hydrous and anhydrous lanolin.

VOLATILE or ESSENTIAL OILS give their characteristic odour and taste to the plant containing them. These are obtained from various plants, being present in the flowers, fruits, seeds and leaves, usually by distillation and rarely by pressure as lemon oil. These are (i) soluble in chloroform and solvent ether and to a less extent in alcohol : (ii) slightly soluble in water also to which they impart their characteristic smell and taste and lighter than water : (iii) do not leave any greasy mark on paper : (iv) mostly inflammable : (v) cannot be saponified and (vi) emulsified with difficulty : (vii) taken internally, not oxidised in the body but excreted mainly combined with glycuronic acid and (viii) on keeping exposed to air, do not become rancid but tends to resinify.

Their chemical composition varies, consisting mainly of terpenes and terpene derivatives. These may be containing (i) *Aldehydes* as cinnamic aldehyde in cinnamon oil. (ii) *Esters* as methyl salicylate in oil of winter green. (iii) *Alcohols* as menthol in oil of peppermint. (iv) *Phenols*, as eugenol in oil of cloves or (v) *Ketones*, as carvone in oil of caraway.

B.P. contains 17 volatile oils.—*Olei amygdalæ volatile purificatum*, anethi, anisi, cajuputi, cari, caryophylli, chenopodii, cinnamomi, coriandri, eucalypti, lavandulæ, limonis, menthæ piperitæ, myristicæ, rosmarini and terebinthinæ.

A few are formed by destructive distillation of certain plants such as creosote and oils of cade and tar : called *Empyreumatic oils*.

Certain solid bodies are prepared from volatile oils. These are called *stearoptenes* : camphor, menthol and thymol.

Oleo resins are natural products of resin dissolved in volatile oils as copaiba.

Resins are brittle, non-volatile, solid substances, being the oxidation products of terpenes or volatile oils and when obtained from the plant exudates, these contain other proximate principles also.

These are soluble in alcohol and alkalies and are precipitated by water. Therefore in various tinctures these are dissolved by alcohol, chloroform, ether or an alkali as in Tinct. Benzoin. Co. When ordered in a mixture, the resin should be suspended with a mucilage.

Several drugs contain resin, one such being cannabis indica. The *resins in the B.P.* are podophyllum and ipomoea or scammony resins.

Saponins are a group of substances, generally glycosides, which are soluble in water, can emulsify oils and form froth when shaken with water. On hydrolysis, these yield sugar and sapogenin.

Quillaia bark and Senega root contain powerful saponins.

Tannins are a group of phenol derivatives occurring in many plants, especially in their barks and leaves.

These make inky solution with iron and precipitate heavy metallic salts, alcohols and protein. These are soluble in water, glycerin and in alcohol.

It is important to remember that the following 8 in B.P. contain tannin : Catechu, cinnamon bark, digitalis, ergot, hamamelis, ipecacuanha, krameria and rhubarb root.

Waxes are combinations of fatty acids and monohydric alcohol, and are more solid with higher melting point than fats and cannot be saponified.

One much used is yellow or white beeswax. The others are hard and soft paraffins.

Synthetic preparations as cetostearyl alcohol and sodium lauryl sulphate may be included here.

PHARMACEUTICAL PROCESSES

Some of the drugs in the Pharmacopœia are well defined single entities but others are in impure and crude state. In order to make these substances into forms suitable for therapeutic administration, these are subjected to various preliminary treatments, as follows :

Bruising—This is the process of smashing up the different parts of a medicinal plant either by a pounding machine or iron pestle and mortar so that the various solvent extractives may have a freer access.

Calcination.—Some inorganic drugs are put into a crucible in a furnace and strongly heated to drive out all moistures and volatile matters.

Magnesia, lime and red mercuric oxide are prepared in this way from their respective carbonates.

Clarification.—This is the process of removing suspended matters to give the preparation a transparent and elegant look.

This is done by filtration, high speed centrifugalisation, depuration, (the preparation, as honey, is gently heated to form a scum at the top which is removed by filtration) and by shaking with animal charcoal and filtration (the colouring matter is removed in this way).

Crystallisation—This is done to separate out soluble matters in the form of crystals by heating and subsequent cooling of a concentrated solution, by sublimation, chemical precipitation or by fusion as of some metals.

Decoction.—A coarsely bruised drug is boiled in water in enamelled or tinned pots with covers for a definite period and then strained : should be used fresh unless has a preservative.

Desiccation.—This is a process of drying vegetable or other drugs in a chamber of definite heat.

Dialysis.—This is a process sometimes used to separate crystalloids (alkaloids, salts etc.) from colloids (extractives), the former passing out through an animal membrane. The difference in the rate of diffusion separates the crystalloids from the colloids.

Distillation.—A liquid substance is put into a closed vessel called *still* and heated. The vapour is taken out of it by a tube and condensed by cold application. The condensed fluid is called the *distillate* and what is left is the *residue*. Sometimes one or the other or both are used in medicine.

Sometimes this distillation is done at different temperatures and the distillate of each is collected separately. This is called *fractional distillation*. In this way, different substances are removed from crude petroleum, coal tar and certain volatile oils.

Sometimes a dry organic substance is heated in a still till all the volatile principles are eliminated. The residue left is carbon in more or less impure state. This is called *destructive distillation*. By this method, acetic acid, acetone, methyl alcohol, creosote and other organic matters are obtained as distillate from wood. Coal-tar, ammonia and a gas for burning purposes are obtained from coal.

Elutriation is a method of separation of the coarser particles of a powder from the finer ones. The whole powder is shaken up with water : after the coarse particles have settled, the fluid is decanted off and the next finer ones now settle.

Expression.—This is the process of pressing out juice or oil from various plant products or of separating the liquid from the marc in a tincture.

Exsiccation is removal of water of crystallisation from crystalline salts by heating in water bath, water oven or more commonly air oven and sand bath.

Fusion : Liquefaction.—A solid substance is liquefied by heating it in a crucible or a suitable vessel ; necessary for the preparation of caustic sticks, plasters, suppositories and certain ointments.

Granulation.—A concentrated solution of a chemical substance is heated with constant stirring : the moisture is largely removed and a granular powder forms.

Effervescent granules (*Granulæ Effervescentes*).—The ingredients, citric and tartaric acids and sodium bicarbonate (with other medicaments if any) are dried, mixed and placed in a suitable vessel at 95° to 105°. The agglomerated mixture is passed through a sieve of suitable mesh.

Ignition or incineration.—Organic substances are strongly heated with free access of air till all carbonaceous matter is burnt off leaving a residue (ash). Organic salts of alkali metals such as benzoates, citrates, salicylates and tartrates are ignited to leave carbonate ash.

Infusion.—Moderately comminuted drugs in a muslin bag are suspended with a thread from the lid of the infusion pot and soaked in hot or cold distilled water as directed.

Levigation.—A solid substance is ground with water thoroughly till it is made into a paste and then dried up.

Lixiviation.—The soluble matter from ashes of any substance is extracted with water. The solution is called “*lye*.”

Maceration.—A ground up drug is soaked in a solvent (commonly alcohol or water), for about seven days, which is agitated from time to time. The fluid is expressed from it and filtered.

This filtrate may subsequently be concentrated by heat. Many tinctures and extracts are made in this way.

Percolation.—A ground up drug is soaked in the menstruum, the solvent to be used, for 4 hours in a closed vessel and is then put into a cylindrical container having an opening at the bottom, called percolator, and more solvent is poured on the top. As the fluid trickles through, the bottom is closed and kept aside for 24 hours. The percolation is now allowed to proceed on slowly and the fluid is collected into the receiving vessel at the bottom.

Marc is the undissolved residue left after extraction of the soluble principles. Many tinctures and liquid extracts are prepared in this way.

Repercolation.—Here the first percolated fluid is used for the second time on a fresh lot of the same drug in the percolator and this process may be repeated several times.

The liquid extract of *Colchicum* is prepared in this way.

Scaling.—A concentrated solution of the drug is put into a glass plate and allowed to dry up. A thin solid film is formed on the plate and this is broken up into thin scales.

Iron and ammonium citrate and iron and quinine citrate are scaled in this way and hence are called *scale preparations*.

Sifting.—A powdered drug is made to pass through a sieve containing parallel wires of various closeness and powders of different fineness are obtained.

Coarse powder (10/44),—all the particles pass through No. 10 and not more than 40% through No. 44 sieve. In the same way, *moderately coarse* (22/60), *moderately fine* (44/85), *fine* (85) and *very fine* (120) powders are obtained, the figures indicating sieve number.

Solvents.—Those in frequent use are water, ethyl alcohol, glycerin, solvent ether, chloroform, petroleum, benzene, acetone and acetic acid.

These with a solid substance form a solution which is either *simple* a specified amount of it being dissolved in the solvent or *saturated*, containing as much of the solid as the solvent can dissolve at the normal temperature and pressure.

Of these *water* is most frequently used because it can dissolve the largest number of substances. Next comes *alcohol* which also dissolves many and has the additional advantage of being a preservative also. Therefore, many vegetable drugs as extracts or tinctures are prepared with it. *Glycerin* is a solvent for borax and phenol and is a preservative for substances like pepsin, tannin and starch. *Solvent ether* is used for dissolving certain oils and fats as in preparing extract of male fern. Solvent *ether* and *chloroform* are used as solvents for alkaloids in drug assays and *acetic acid* is a solvent for certain substances and for making oxymel, syrup and vinegar of squill and tincture of ipecacuanha. *Light petroleum* is a good solvent of oils, fats and resins in making liquid extracts of colchicum and ergot.

Standardisation.—The Pharmacopœia directs that certain powerful medicinal preparations must contain a fixed quantity of their chief active principles.

(1) The following drugs are STANDARDISED CHEMICALLY to contain the stated amount of the active principles.

(i) *Belladonna*.—Leaves, not less than 0.3% of alkaloids; Dry extract, 1%; and tincture, 0.03% alkaloids of leaves. Roots, not less than 0.4% of total alkaloids. Liquid extract, 0.75%; Liniment, 0.375% of total alkaloids of roots.

(ii) *Colchicum*.—Tincture, 0.03%; Dry Extract, 1%; Liquid Extract, 0.3% and dried Corn not less than 0.25% and seed not less than 0.3% of colchicine.

(iii) *Ergot*.—Ergot, 0.2%; Ergot prepared 0.2%; Liquid Extract, 0.06% of total alkaloids calculated as ergotoxine.

(iv) *Filix mas*.—Liquid Extract 25% of filicin.

(v) *Hyoscyamus*.—Leaves, 0.05%; Dry Extract, 0.3% and Liquid Extract, 0.05% of total alkaloids; Tincture, 0.005%.

(vi) *Ipecacuanha*.—Root not less than 2%; Liquid Extract, 2% and Tincture, 0.1% of total alkaloids calculated as emetine.

(vii) *Nux vomica*.—Nut, 1.2%; Dry Extract, 5%; Liquid Extract, 1.5% and Tincture, 0.125% of Strychnine.

(viii) *Opium*.—Raw Opium, not less than 9.5%; Powdered Opium 10%; Tincture, 1%; Camphorated tincture, 0.05%; Powdered Ipecac. and Opium 1% and Powdered Crete Arom. c. Opio, 0.25% of morphine.

(ix) *Stramonium*.—Powder, 0.25%; Liquid Extract, 0.25%; Dry Extract, 1% and Tincture, 0.025% of alkaloids calculated as hyoscyamine.

(2) The following are standardised by BIOLOGICAL ASSAY.

Aneurine hydrochloride; antitoxins of diphtheria, gas gangrene and tetanus; digitalis leaves and tincture; gonadotrophins chorionic and serum; heparin; insulin and zinc protamine insulin; neo- and sulpharsphenamine; penicillin; pituitary (posterior lobe extract), strophanthus, old tuberculin and vitamins A and D.

The common principle involved is that of comparison of the substance concerned with the standard preparation so as to determine how much of a sample to be tested produces the same biological effect as by a given quantity, *the unit*, of the standard preparation.—The standards for Great Britain and Northern Ireland are kept at the National Institute of Medical Research, Hampstead, London.

(3) Standardisation is also done by PHYSICAL ASSAY by finding out the specific gravity, melting point, optic rotation, refractive indices and iodine and saponification values.

Sterilisation.—The Pharmacopœia directs the following methods for sterilisation of a solution for injection :

(a) *Sterilisation by Autoclaving.*—The solution or the preparation is put in suitable containers and sealed. If the volume of each container does not exceed 100 ml., it is autoclaved as above for 30 minutes : if more, for a longer period, to ensure that the whole solution is maintained at 115° to 116° for 30 minutes.

(b) *Sterilisation by heating with a Bactericide.*—The medicament is dissolved in 0·2% w/v sol. of chlorocresol or 0·002% w/v sol. of phenyl mercuric nitrate in water for injection. The container is sealed and if the quantity does not exceed 30 ml., it is heated at 98° to 100° for 30 minutes. If more, heated for a longer period to ensure that the whole solution is maintained at the above temperature for 30 minutes.

(c) *Sterilisation by filtration.*—The solution is filtered through a sterile bacteria-proof filter, put into sterile containers and sealed.

(d) *Sterilisation of Oily Solutions and Suspensions.*—The preparation (the solution or suspension in oil or ethyl oleate) is put into the final container and sealed. This is heated to 150° for one hour. If the content exceeds 30 ml., it is heated for a longer period as described above. If likely to decompose at 150°, the oil is sterilised as above, to this the medicament is dissolved under aseptic precaution and put in a sterile container and sealed.

Sublimation.—A solid substance is first vaporised by heat and then allowed to condense either into a mass (as mercuric chloride) or a fine powder (as sublimed sulphur).

Trituration.—This is the process of rubbing down solid substances into finer particles with the help of pestle and mortar.

Salts and crystalline substances are powdered in a wedgwood mortar and a vegetable product is best ground in an iron mortar.

WEIGHTS AND MEASURES

Imperial System

| Weight | | Symbol |
|--------------|-----|---------------------------------|
| One grain | ... | gr. |
| 437·5 grains | ... | 1 oz. |
| 16 ounces | ... | one pound (<i>libra</i> , lb.) |

| Capacity | Symbol |
|---------------------|--|
| One minim ... | ... min. or m. |
| 60 minims ... | ... 1 fl. dr. |
| 8 fluid drachms ... | ... 1 fl. oz. |
| 20 fl. ounces ... | ... 1 pint (pt., <i>octarius</i> , o.) |
| 8 pints ... | ... 1 gallon (<i>congius</i> , c.) |

The special symbols $\frac{3}{4}$ for drachm and $\frac{3}{8}$ for ounce are no longer official and may not be used.

Relation of Measures by Capacity to Weight :

It is important to know that one minim of distilled water by volume at 16.7°C is 0.91146 grain by weight : so one fluid ounce of distilled water at 16.7°C weighs 437.5 grains. Therefore 1% solution is 437.5 grains in 100 fl. oz. of water or 4.375 grains in 1 fl. oz. which is again equivalent to one gr. in $(480 \div 4.375)$ minims. This is 109.7 min. (roughly 110 min.) containing one grain.

When making lotions of different strengths, multiply 4.375 by the required strength which is again multiplied by the required quantity in ounce : the result will be the dry substance to be used in grain. This is graphically represented as follows :

Lotion = $4.375 \times PQ$, P representing the percentage and Q the quantity in grains per ounce. Thus 5 fl. oz. of 1 in 1000 lotion contains $4.375 \times 1/10 \times 5$ gr. of the dry substance or 2.1875 grains.

Metric System

WEIGHT :

One Gramme (g. = weight of one millilitre or ml. of water at 4°C) is taken as the unit. Its fractions, 1/10, 1/100, and 1/1000th are respectively called decigram (dg.), centigram (cg.), and milligram (mg.). 1/1000th of milligram is microgram (μ or μ g). Its multiples in 10, 100, and in 1000 are called dekagram (dag.), hectogram (hg.) and kilogram (kg.). (In writing prescriptions, "G" should be used for gramme). The measures microgram, milligram, gramme and kilogram are only official.

CAPACITY OR VOLUME

One millilitre (mil. or ml) or cubic centimetre (1 c.c.), the volume of one grm. of water, is the usual unit. Its fractions 1/10th and 1/100th are called decimil and centimil.

Its multiples, in 10, 100 and in 1000 are called respectively centilitre (cl.), decilitre (dl.) and litre (l.). Here 1% solution is 1 grm. in 100 ml., and the rest are calculated accordingly.

The British Pharmacopœia uses the following symbols for percentage solutions :

Per cent. W/W = the weight in weight is active substance in
 gm. per 100 grms. of product.

Per cent. W/V = the weight in volume is active substance in
 gm. per 100 mil. of product.

Per cent. V/V = the volume in volume is active substance in
 mil. per 100 mil. of product.

Per cent. V/W = volume in weight is active substance in
 mil. per 100 grms. of product.

If the strength of a solution is expressed as parts of the dissolved substance in parts of the solution, the solids and gases should be taken by weight in grammes and the liquid by volume in millilitres.

LENGTH :

One metre (m.) is the unit. Its fractions, 1/100th and 1/1000th are centimetre (cm.) and millimetre (mm.). 1/1000th of millimetre is one micron (μ) and 1/1000th of a micron is one millimicron ($m\mu$).

CONVERSION OF METRIC INTO IMPERIAL SYSTEM

1 kilogram.=2 lbs. $3\frac{1}{2}$ oz.
 1 gramme=15.432 grains.
 60 milligram.=1 gr.
 10 milligram.= $\frac{1}{6}$ gr.
 5 milligram.= $\frac{1}{12}$ grain.
 6 milligram.= $\frac{1}{10}$ grain.
 1 milligram.= $\frac{1}{60}$ gr.
 1 grain=0.064 grm.

1 ounce=28.35 grm.
 1 millilitre=16.89 min.
 1 litre (1000 c.c.)=35.19 fl. oz.
 1 minim=0.059 ml.
 1 fl. ounce=28.41 ml.
 1 metre=39.3 inches
 1 millimetre=0.039 inches.
 1 inch=2.6 centimetre.

DOMESTIC MEASURES

1 tea-spoonful=a little over 1 fl. dr.
 1 dessert-spoonful=about 2 fl. dr.
 1 table-spoonful= $\frac{1}{2}$ fl. oz.
 1 wine-glassful=about $1\frac{1}{2}$ to 2 fl. oz.
 1 tea-cupful=about 7 to 8 fl. oz.
 1 tumblerful=about 15 to 20 fl. oz.

A drop of a liquid is sometimes taken for a minim. But as the size of the drop varies with the density of the fluid, no powerful medicine should be measured by the drop method.

Indian Weights.—One tola (weight of one rupee) is 180 grains. One nickel 2 anna bit is 90 grains and one nickel anna bit is 60 grains. 5 tolas make a chatta or 4 kauchas : 4 chattas=one poa : 4 poas=one seer. 40 seers=one maund. One ounce=about 2.5 tolas or $\frac{1}{2}$ chatta.

PHARMACOPŒIAL PREPARATIONS

These may be called *Official galenicals* after Galen (A.D. 130 to 230), the Father of Pharmacopœia.

1. **Acetum**, 1.—The active principles of the drug are extracted by maceration or digestion with dilute acetic acid.

Acetum Scillæ (Squill 100 g. and dilute acetic acid 1000 ml.) : 10% w/v of squill. Dose, 10 to 30 min. or 0.6 to 2 ml.

2. **Acida Diluta**, 4.—Strong acids are diluted with distilled water.

Acidum Aceticum Dilutum (Acetic acid 182 g. and distilled water 818 g., 6%), *Acidum Hydrochloricum Dilutum* (Hydrochloric acid 274 g. and distilled water 726 g., 10% of hydrochloric acid). Dose, 10 to 120 min. or 0.6 to 8 ml. : *Acidum Hypophosphorosum Dilutum* (10%) : Dose, 5 to 15 min. or 0.3 to 1 ml., *Acidum Phosphoricum Dilutum* (Phosphoric acid 112 g. and distilled water 888 g., 10%) : Dose, 5 to 60 min. or 0.3 to 4 ml.

3. **Adeps**, 2.—Lard (adepts) and wool fat (adepts lanæ).

From the first, *Adeps Benzoinatus* (Benzoin Siam 20 g. and lard 1000 g.) : from the second, *Adeps Lanæ Hydrosus* (Wool fat 700 g. and distilled water 300 ml.).

4. *Alcohol Diluta*, 6.—*Alcohol 90%* (Alcohol 95% 947 ml. and distilled water to 1000 ml.). *Alcohol 80%* (Alcohol 95% 842 ml. and distilled water to 1000 ml.). *Alcohol 70%* (Alcohol 95% 737 ml. and distilled water to 1000 ml.). *Alcohol 60%* (Alcohol 95% 632 ml. and distilled water to 1000 ml.). *Alcohol 50%* (Alcohol 95% 526 ml. and distilled water to 1000 ml.). *Alcohol 45%* (Alcohol 95% 474 ml. and distilled water to 1000 ml.).

5. *Aquae*, 7.—These are as follows.—

(a) *Aquae Aromaticæ* or Aromatic waters are prepared by making a solution of a volatile oil in 500 times of distilled water by shaking for 15 minutes or preliminary trituration with a sufficient quantity of talc or by dilution of concentrated waters with 39 times of distilled water.

Aquæ Aromaticæ Concentratæ are prepared by dissolving 20 ml. of the volatile oil in 600 ml. of alcohol (90%), slowly adding distilled water to make 1000 ml. and clarifying. *Aquæ Anethi Concentrata*, *Cinnamomi Concentrata*, *Menthæ Piperitæ Concentrata* are prepared in the above way. Dose, 5 to 15 min. or 0.3 to 1 ml. *Aqua Camphoræ* (Camphor 1 g., alcohol 90%, 2 ml. and distilled water to 1000 ml.) Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

(b) *Aqua Chloroformi* (Chloroform 2.5 ml. and distilled water to 1000 ml.). Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

(c) *Aqua Destillata* (prepared by distillation of potable water). *Aqua Pro Injectione* (after rejecting the first portion, distilled water is put in a closed container and autoclaved).

6. *Cataplasma*, 1.—This is a soft, pasty substance, to be applied hot, of the nature of a poultice.

Cataplasma Kaolini (Heavy kaolin dry 527 g., boric acid 45 g., methyl salicylate 2 ml., oil of peppermint 0.5 ml., thymol 0.5 g. and glycerin 425 g.).

7. *Collodium*, 1.—This is a solution of pyroxylin in solvent ether : if applied externally, is evaporated into a thin protective film.

Collodium Flexile, Collodion (Pyroxylin 20 g., colophony 30 g., castor oil 20 g., alcohol 90%, 240 ml. and solvent ether to produce 1000 ml.).

8. *Cremora*, 2, are white milky thickish substances, mainly used locally on the affected area.

Cremor Penicillini (Penicillin sodium or calcium a sufficient quantity, emulsifying wax 7 g., hard paraffin 5 g., liquid paraffin 41 g., chlorocresol 0.1 g., and distilled water 47 ml. freshly prepared) : usual strength is 500 units per g.

Cremor Penicillini Sterilisatus (The above without chlorocresol and with water for injection) : the base is sterilised by autoclaving at 115° for 30 minutes and then penicillin is added aseptically ; strength as above.

9. *Elixir*, 1.—This is a sweet aromatic preparation containing the active principles of the drug with aromatics, sweetening agents and alcohol (90%).

Elixir Cascarae Sagradae (Cascara sagrada 1000 g., liquorice 125 g., light mag. oxide 150 g., sodium saccharin 1 g., oil of coriander 0.15 ml., oil of anise 0.2 ml., alcohol 90%, 12.5 ml., glycerin 300 ml. and distilled water to 1000 ml.). Dose, 30 to 60 min. or 2 to 4 ml.

10. *Emulsiones*, 4.—These are suspensions of oils in water with gums or with gum and saponin: to this flavourings have also been added.

(i) *Emulsio Chloroformi* (Chloroform 50 ml., liq. ext. of quillaia 1 ml., mucil. of tragacanth 50 ml. and distilled water to 1000 ml. and (ii) *Emulsio Menthæ Piperitæ* (Oil of peppermint 100 ml., liq. ext. of quillaia 2.5 ml. and distilled water to 1000 ml.). Dose of both, 5 to 30 min. or 0.3 to 2 ml. (iii) *Emulsio Olei Morrhuae* (Cod-liver oil 500 ml., acacia 125 g., tragacanth 7 g., purified volatile oil of bitter almond 1 ml., sodium saccharin 0.1 g., chloroform 2 ml. and distilled water to 1000 ml.). Dose, 120 to 360 min. or 8 to 24 ml., daily. (iv) *Emulsio Paraffini Liquidi* (Liquid paraffin 500 ml., acacia 125 g., tragacanth 5 g., glycerin 125 ml., sod. benzoate 5 g., vanillin 0.5 g., chloroform 2.5 ml. and distilled water to 1000 ml.). Dose, $\frac{1}{4}$ to 1 fl. oz. or 8 to 30 ml.

11. *Extracta*, 28.—These are the concentrated preparations of the active principles of some drugs and are either *liquid*, *semi-liquid* or *solid*. The strength of the liquid extracts containing no powerful substance is, one part by weight of the crude drug producing one part by volume of the extract. But if there is a toxic constituent, the strength should be adjusted to the percentage of the active substance. Soft extracts are more difficult to adjust in the above way. These are prepared as follows.—

(i) *Aqueous Extracts*.—The drug is extracted with cold, hot or boiling water and evaporated to the required consistency, as Ext. Casc. Sagr. Sicc. In preparing Ext. Glycyrrhizæ and Ext. Glycyrrhizæ liq., Chloroform water is used which acts as a preservative.

(ii) *Alcoholic Extracts*.—Alcohol of various strengths is used in different preparations and the extractives are evaporated to the required consistency, as Ext. Bellad. Sicc.

(iii) *Ethereal Extracts*.—Solvent ether is used as the extractive, as in Ext. Filic. Liq.

These may be further classified as *solid* and *liquid* extracts. The solid extract is made of different consistency: the evaporation is stopped when the preparation is either a soft mass (*soft extract*) or it is completely dry (*dry extract*).

Of the dried extracts, those of Belladonna, Colchicum, Hyoscyamus, Nux Vomica and Stramonium: of the liquid extracts, those of Belladonna, Colchicum, Ergot, Male fern, Hyoscyamus, Ipecacuanha, Liver, Malt and Codliver oil, Nux Vomica and Stramonium are *standardised*. See p. 33.

If any of these contains less than $\frac{1}{4}$ of its weight of alcohol (90%), in tropical countries it may be increased up to that amount to prevent fermentation and consequent deterioration. *All liquid extracts except of Malt and Male fern contain alcohol.*

SOLID EXTRACTS, 11.—(1) *Extractum Belladonnae Siccum* (Belladonna herb 1000 g. or sufficient quantity and alcohol 70%,

finally to contain 1% of total alkaloids). Dose, $\frac{1}{4}$ to 1 gr. or 15 to 60 mg.

(2) *Extractum Cascaræ Sagradæ Siccum* (Powder is exhausted with distilled water by percolation and concentration). Dose, 2 to 8 gr. or 0.12 to 0.5 G.

(3) *Extractum Colchici Siccum* (Colchicum corm 1000 g., alcohol 60% and lactose sufficient quantity): contains 1% of colchicine. Dose, $\frac{1}{6}$ to $\frac{1}{2}$ gr. or 10 to 30 mg.

(4) *Extractum Colocynthidis Compositum* (Colocynth. 270 g., aloes 560 g., ipomœa resin 185 g., curd soap 140 g., cardamom 45 g., and alcohol 60%, 7000 ml.; remove alcohol and evaporate to dryness). Dose, 2 to 8 gr. or 0.12 to 0.5 G.

(5) *Extractum Fellis Bovini* (90% Alcoholic extract of ox bile evaporated to a firm extract). Dose, 5 to 15 gr. or 0.3 to 1 G.

(6) *Extractum Glycyrrhizæ* (Liquorice exhausted with chloroform water by percolation: evaporated to firm extract). Dose, 10 to 30 gr. or 0.6 to 2 G.

(7) *Extractum Hamamelidis Siccum* (Hamamelis 1000 g., and alcohol 45%, a sufficient quantity: percolate and evaporate the residue to dryness).

(8) *Extractum Hyoscyami Siccum* (Hyoscyamus powder 1000 g., percolated with 70% alcohol, each sufficient quantity): contains 0.3% of total alkaloids of hyoscyamus. Dose, $\frac{1}{4}$ to 1 gr. or 16 to 60 mg.

(9) *Extractum Kramerizæ Siccum* (Krameria exhausted with distilled water). Dose, 5 to 15 gr. or 0.3 to 1 G.

(10) *Extractum Nucis Vomizæ Siccum* (Nux vomica 1000 g., calcium phosphate and alcohol 70% q.s.): contains 5% of strychnine. Dose, $\frac{1}{4}$ to 1 gr. or 15 to 60 mg.

(11) *Extractum Stramonii Siccum* (Stramonium 1000 g., alcohol 95% and starch q. s.) contains 1% of stramonium alkaloids calculated as hyoscyamine. Dose, $\frac{1}{4}$ to 1 gr. or 15 to 60 mg.

For post-encephalitic and similar conditions, 1 to 8 gr. or 60 to 500 mg.

DOSE SCHEDULE.— $\frac{1}{6}$ to $\frac{1}{2}$ gr. (Ext. Colch. Sicc.): $\frac{1}{4}$ to 1 gr. (Ext. Bellad. Sicc., Hyosey. Sicc., Nuc. Vom. Sicc. and Stramon. Sicc.): 2 to 8 gr. (Ext. Casc. Sagr. Sicc. and Colocynth. Co.): 5 to 15 gr. (Ext. Fell. Bov. and Kramer Sicc.): 10 to 30 gr. (Ext. Glycyrrh.). No dose (Ext. Hamam. Sicc.).

LIQUID EXTRACTS, 17.—(1) *Extractum Belladonnæ Liquidum* (Belladonna root 1000 g., and alcohol 80% sufficient quantity to contain 0.75% w/v of total alkaloids).

(2) *Extractum Cascaræ Sagradæ Liquidum* (Cascara sagrada 1000 g., alcohol 90% 250 ml. and distilled water to 1000 ml.) Dose, 30 to 60 min. or 2 to 4 ml.

(3) *Extractum Colchici Liquidum* (Colchicum seed 1000 g., and alcohol 60% sufficient quantity, percolated to obtain 1000 ml.): contains 0.3% w/v of colchicine.

(4) *Extractum Ergotæ Liquidum* (Ergot 1000 g., and tartaric acid and alcohol 50% q.s. to contain 0.06% w/v of alkaloids as ergotoxine). Dose, 10 to 20 min. or 0.6 to 1.2 ml.

(5) *Extractum Filicis* (Male fern exhausted with solvent ether by percolation) : contains 25% w/w of filicin. Dose, 45 to 90 min. or 3 to 6 ml.

(6) *Extractum Glycyrrhizæ Liquidum* (Liquorice 1000 g., chloroform water and alcohol 90% q.s.). Dose, 30 to 60 min. or 2 to 4 ml.

(7) *Extractum Hamamelidis Liquidum* (Hamamelis 1000 g. and alcohol 45% sufficient quantity to 1000 ml.).

(8) *Extractum Hepatis Liquidum* (Selected fraction of an alcoholic extract of ox or sheep liver in a mixture of glycerin, alcohol (95%) and distilled water) : 1 fl. oz. equals 8 oz. of fresh liver. Dose, 1 fl. oz. or 30 ml.

(9) *Extractum Hyoscyami Liquidum* (Hyoscyamus 1000 g. and alcohol 70% q. s.) : contains 0.05% w/v of total alkaloids. Dose, 3 to 6 min. or 0.2 to 0.4 ml.

(10) *Extractum Ipecacuanhæ Liquidum* (Ipecacuanha 1000 g., and alcohol 80% q.s.). Dose, $\frac{1}{2}$ to 2 min. or 0.03 to 0.12 ml. : as emetic, 10 to 30 min. or 0.6 to 2 ml.

(11) *Extractum Malti* (Malted grain of barley or/and of wheat are digested and extracted with water at a temperature of about 55°). Dose, 60 min. to 1 fl. oz. or 4 to 30 ml. daily.

(12) *Extractum Malti cum Oleo Morrhue* (Malt extract 900 g., and cod-liver oil 100 g.). Cod-liver oil is 10% w/w and 15% v/v. Dose, 60 min. to 1 fl. oz. or 4 to 30 ml. daily.

(13) *Extractum Nucis Vomice Liquidum* (Nux vomica 1000 g. and alcohol 70% and 45% q.s. exhausted by percolation) ; contains 1.5% w/v of strychnine. Dose, 1 to 3 min. or 0.06 to 0.2 ml.

(14) *Extractum Quillaie Liquidum* (Quillaia 1000 g. and alcohol 45% to 1000 ml. Percolated and concentrated by evaporation).

(15) *Extractum Senegæ Liquidum* (Senega 1000 g., dilute solution of ammonia q. s. and alcohol 60% to 1000 ml.). Dose, 5 to 15 min. or 0.3 to 1 ml.

(16) *Extractum Sennæ Liquidum* (Senna 1000 g., oil of coriander 6 ml., alcohol 90% 250 ml. and chloroform water and distilled water q.s.). Dose, 10 to 30 min. or 0.6 to 2 ml.

(17) *Extractum Stramonii Liquidum* (Stramonium 1000 g. and alcohol 45% q. s.) ; contains 0.25% w/v of stramonium alkaloids. Dose, $\frac{1}{2}$ to 3 min. or 0.03 to 0.2 ml.

DOSE SCHEDULE.— $\frac{1}{2}$ to 2 min. (Ext. Ipecac. Liq.) : $\frac{1}{2}$ to 3 min. (Ext. Stramon. Liq.) : 1 to 3 min. (Ext. Nuc. Vom. Liq.) : 3 to 6 min. (Ext. Hyoscy. Liq.) : 5 to 15 min. (Ext. Seneg. Liq.) : 10 to 20 min. (Ext. Ergot. Liq.) : 10 to 30 min. (Ext. Ipecac. Liq., Senn. Liq.) : 30 to 60 min. (Ext. Casc. Sagr. Liq. and Glycyrrh. Liq.) : 45 to 90 min. (Ext. Filic.) : 60 min. to 1 fl. oz. (Ext. Malt. and Malt. c. Ol. Morrh.) : 1 fl. oz. (Ext. Hepat. Liq.) : No dose. (Ext. Bellad. Liq., Colch. Liq., Hamam. Liq. and Quill. Liq.).

12. *Gelatinum*, 1.—Ointment-like substance is prepared for external use as a non-irritating protective.

Gelatinum Zinci, Unna's paste. (Zinc oxide 150 g., gelatin 150 g., glycerin 350 g. and distilled water 350 ml. or q.s.).

13. **Glycerina**, 5.—Drugs are dissolved in glycerin and are mostly used externally.

Glycer. Acid. Boric. (Boric acid 310 g. and glycerin to 1000 g. or 31%) : *Glycer. Acid. Tann.* (Tannic acid 150 g. and glycerin 850 g.) : *Glycer. Amyli* (Wheat starch 85 g., distilled water 170 ml. and glycerin 745 g.) : *Glycer. Boracis* (Borax 120 g. and glycerin 880 g. or 12%) and *Glycer. Phenol.* (Phenol 160 g. and glycerin 840 g. or 16%).

14. **Infusa**, 14.—Boiling (or cold, in cases of calumba and quassia) distilled water is poured on the drugs in a covered vessel and kept for 15 minutes and calumba and senega kept for $\frac{1}{2}$ hour and then strained. The filtrate is the fresh infusion. (*Infusa Recens*) and to be used within 12 hours of the preparation. The others are prepared with weak alcohols which act as preservative (*Infusa Concentrata*) and others again by diluting the stocked concentrated infusa with distilled water often at the time of dispensing and used within 12 hours : (the usual *Infusa*). All these have the water-soluble extractives.

(1) Fresh Infusions : (i) *Infusum Calumbæ Recens* (Calumba 50 g. and cold distilled water 1000 ml.) and (ii) *Infusum Quassiae Recens* (Quassia 10 g. and distilled water to 1000 ml.). Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

(2) Concentrated Infusa : (i) *Infusum Aurantii Concentratum* (Dried bitter orange peel 400 g. and alcohol 25% 1350 ml.). Macerate for 48 hours.

(ii) *Infusum Calumbæ Concentratum* (Calumba 400 g., alcohol 90% 250 ml. and cold distilled water q.s. to 1000 ml.).

(iii) *Infusum Caryophylli Concentratum* (Powdered clove 200 g. and alcohol 25% 1100 ml.) : Macerate for 48 hours.

(iv) *Infusum Gentianæ Compositum Concentratum* (Gentian 100 g., dried bitter orange peel and dried lemon peel each 100 g. and alcohol 25% 1200 ml.). Macerate for 48 hours.

(v) *Infusum Quassiae Concentratum* (Quassia 80 g., alcohol 90%, 250 ml. and distilled water to 1000 ml.). Macerate successively three times.

(vi) *Infusum Senegæ Concentratum* (Senega 400 g., dilute solution of ammonia to alkalise and alcohol 25% to 1000 ml.) Percolate and adjust the volume.

(vii) *Infusum Sennæ Concentratum* (Senna fruit 800 g., strong tinct. of ginger 80 ml. and alcohol 20% to 1000 ml.). Dose of each is 30 to 60 min. or 2 to 4 ml. except of concentrated infusion of senna which is 30 to 120 min. or 2 to 8 ml.

(3) The other 7 infusa : *Infusa* (i) *Aurantii*, (ii) *Calumbæ*, (iii) *Caryophylli*, (iv) *Gentianæ Compositum*, (v) *Quassiae*, (vi) *Senegæ* and (vii) *Sennæ* are prepared by diluting corresponding concentrated infusa 125 ml. with distilled water to make 1000 ml. Dose of each is $1\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. except of infusion of Senna which is $\frac{1}{2}$ to 2 fl. oz. or 15 to 60 ml.

15. **Injectiones** 75.—The vehicle is first sterilised and then the active agent is added and sometimes both together

are again sterilised : or the active agent is obtained from sterile sealed ampoules and freshly dissolved in water for injection.

These are for parenteral administration, often subcutaneously, sometimes intramuscularly and occasionally intravenously.

(1) *Injectio Adrenalinae* (Adrenaline 0.1 g., tartaric acid 0.08 g., sodium metabisulphite 0.1 g., sodium chloride 0.8 g. and water for injection to 100 ml.) : autoclaved. Dose, 2 to 8 min. or 0.12 to 0.5 ml. subcutaneously.

(2) *Injectio Ethanolaminae Oleatis* (Ethanalamine 0.91 g., oleic acid 4.23 g., benzyl alcohol 2 ml. and water for injection to 100 ml.). Dose, 30 to 75 min. or 2 to 5 ml. intravenously.

(3) *Injectio Amethocainae Hydrochloridi* (Sterile solution of Amethocaine hydrochloride from a sealed container dissolved in injection of sodium chloride in labelled amount).

(4) *Injectio Aneurinae Hydrochloridi* (Aneurine hydrochloride in water for injection in labelled amount) : sterilised by filtration. Dose, $\frac{1}{6}$ to $\frac{1}{2}$ gr. or 10 to 30 mg.

(5) *Injectio Antimonii et Potassii Tartratis* (Sterile solution of potassium antimonyltartrate in water for injection) : sterilised by autoclaving or by filtration. Dose, of pot. antim. tart. $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. by intravenous injection.

(6) *Injectio Antimonii et Sodii Tartratis* (Sterile solution of sodium antimonyltartrate in water for injection) : autoclaved or filtered. Dose of sod. antim. tart. $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. by intravenous injection.

(7) *Injectio Apomorphinae Hydrochloridi* (Sterile solution of apomorphine hydrochloride in water for injection, containing 0.05% w/v of sodium metabisulphite) : heated with a bactericide or filtered. Dose of apomorphine hydrochloride (emetic) by subcutaneous injection $\frac{1}{32}$ to $\frac{1}{8}$ gr. or 2 to 8 mg.

(8) *Injectio Atropinae Sulphatis* (Sterile solution of atropine sulphate in water for injection : sterilised by heating with a bactericide or by filtration). Dose of atropine sulphate by subcutaneous injection $\frac{1}{240}$ to $\frac{1}{60}$ gr. or 0.25 to 1 mg.

(9) *Injectio Bismuthi* (Precipitated bismuth 5 g., dextrose 1.25 g., chlorocresol 0.025 g. and water for injection 23.5 ml.) : sterilised by heating in an autoclave. Dose, 8 to 15 min. or 0.5 to 1 ml. intramuscularly.

(10) *Injectio Bismuthi et Sodii Tartratis* (Sterile solution of sodium bismuthyl tartrate in water for injection, reaction adjusted to pH 5.5 : sterilised by autoclaving or by filtration. Dose by intramuscular injection, of sodium bismuthyltartrate 1 to 3 gr. or 60 to 200 mg.

(11) *Injectio Bismuthi Oxychloridi* (Bismuth oxychloride 10 g.; dextrose 5 g., chlorocresol 0.2 g. and water for injection to 100 ml. : sealed container is heated to 98° to 100° for 30 minutes. Dose, 15 to 30 min. or 1 to 2 ml. intramuscularly.

(12) *Injectio Bismuthi Salicylatis* (Bismuth salicylate 10 g., camphor 1 g., phenol 1 g. and arachis oil to 100 ml.). Sterilise

the oil by heating at 150° and add the rest. Dose, 10 to 20 min. or 0·6 to 1·2 ml. intramuscularly.

(13) *Injectio Caffeinae et Sodii Benzoatis* (Sterile solution of caffeine and sodium benzoate in water for injection) : sterilised by autoclaving or by filtration. Dose of caffeine-sodium benzoate is 2 to 5 gr. or 0·12 to 0·3 G. subcutaneously.

(14) *Injectio Calcii Gluconatis* (Calcium gluconate 10 g. and water for injection 95 ml.) : sterilised by autoclaving. Dose, 150 to 300 min. or 10 to 20 ml. intravenously or intramuscularly.

(15) *Injectio Carbacholi* (Sterile solution of carbachol in water for injection) : sterilised by autoclaving or by filtration. Dose, 1/240 to 1/120 gr. or 0·25 to 0·5 mg. subcutaneously.

(16) *Injectio Deoxycortoni Acetatis* (Sterile solution of deoxycortone acetate in ethyl oleate or a suitable oil) : sterilised by heating at 150° for one hour. Dose, 1/30 to 1/6 gr. or 2 to 10 mg. intramuscularly.

(17) *Injectio Dextrosi* (Sterile solution of dextrose in water for injection) : sterilised by autoclaving or by filtration. Usually a 5% w/v solution is dispensed.

(18) *Injectio Digoxini* (Fresh solution of sterile alcoholic solution of digoxin in 9 times of its volume of injection of sodium chloride). Alcoholic solution contains digoxin 50 mg. and alcohol (70%) to 100 ml. Dose of digoxin injection, 150 to 300 min. or 10 to 20 ml.

(19) *Injectio Diodoni* (Sterile solution of diethanolamine salt of 3 : 5-diiodo-4-pyridone-*N*-acetic acid in water for injection) : sterilised by filtration or autoclaving. Dose : for adult, 300 min. or 20 ml. : for a child, 120 to 150 min. or 8 to 10 ml. : for an infant, 30 to 45 min. or 2 to 3 ml. intravenously.

(20) *Injectio Emetinae Hydrochloridi* (Sterile solution of emetine hydrochloride in water for injection) : sterilised by heating with a bactericide or by filtration. Dose, 1/2 to 1 gr. or 30 to 60 mg. daily.

(21) *Injectio Ergometrinæ Maleatis* (Sterile solution of ergometrine maleate in water for injection) : sterilised by autoclaving. Dose, 1/240 to 1/120 gr. or 0·25 to 0·5 mg. intramuscularly ; 1/480 to 1/240 gr. or 0·125 to 0·25 mg. intravenously.

(22) *Injectio Gonadotrophini Chorionici* (Sterile solution prepared by dissolving the contents of a sealed container of chorionic gonadotrophin in water for injection containing 0·5% of phenol). Dose 100 to 500 units by intramuscular injection.

(23) *Injectio Gonadotrophini Serici* (Sterile solution prepared by dissolving the contents of a sealed container of serum gonadotrophin in water for injection containing 0·5% of phenol). Dose, 200 to 1000 units by intramuscular injection.

(24) *Injectio Heparini* (Sterile solution of heparin in injection of sodium chloride) : sterilised by filtration. Dose, 6000 to 12000 units intravenously.

(25) *Injectio Hexobarbitoni Sodii* (Sterile solution of the contents of a sealed container of sodium hexobarbitone in water for injection free from CO_2 , prepared fresh before use). Dose of sodium hexobarbitone intravenously or intramuscularly, 3 to 15 gr. or 0.2 to 1 G.

(26) *Injectio Histaminæ Phosphatis Acidi* (Sterile solution of histamine acid phosphate in water for injection): sterilised by autoclaving or by filtration. Dose of Histamine acid phosphate is 1/120 to 1/60 gr. or 0.5 to 1 mg. subcutaneously.

(27) *Injectio Hyoscinae Hydrobromidi* (Sterile solution of hyoscyne hydrobromide in water for injection): sterilised by heating with a bactericide or by filtration. Dose of Hyoscyne Hydrobromide, 1/200 to 1/100 gr. or 0.3 to 0.6 mg. subcutaneously.

(28) *Injectio Insulini* (A sterile solution of the specific antidiabetic principle of the mammalian pancreas containing 20, 40 or 80 units per ml.). Dose as determined by the physician.

(29) *Injectio Insulini Protaminati cum Zinco* (A sterile suspension of the specific antidiabetic principle of the mammalian pancreas with a suitable protamine and zinc chloride, containing 40 or 80 units per ml.). Dose as determined by the physician.

(30) *Injectio Iodoxyli* (Sterile solution of iodoxylin in water for injection): sterilised by filtration or autoclaving. Dose, 150 to 225 gr. or 10 to 15 G. intravenously.

(31) *Injectio Leptazoli* (Leptazol 10 g., sodium phosphate 0.25 g. and water for injection to 100 ml.): sterilised by autoclaving or by filtration. Dose, 8 to 15 min. or 0.5 to 1 ml. subcutaneously.

(32) *Injectio Menaphthoni* (Sterile solution of menaphthone in ethyl oleate or a suitable oil): sterilised in sealed container by heating at 150° for one hour. Dose, 1/60 to 1/12 gr. or 1 to 5 mg. intramuscularly.

(33) *Injectio Mepacrinae Methanosulphonatis* (Sterile solution of the contents of a sealed container of mepacrine methanesulphonate in water for injection, prepared immediately before use). Dose of Mepacrine methanesulphonate, 1½ to 5 grs. or 0.1 to 0.3 g., intramuscularly.

(34) *Injectio Mersalyli* (Mersalyl 10 g., theophylline 5 g., potassium hydroxide sol. sufficiently and water for injection 100 ml.): sterilised by filtration. Dose, 8 to 30 min. or 0.5 to 2 ml. intravenously or intramuscularly.

(35) *Injectio Morphinae et Atropinae* (Sterile solution of atropine sulphate 0.06 g. and morphine sulphate 1 g. in water for injection to 100 ml.): sterilised by heating with a bactericide or by filtration. Dose, 8 to 15 min. or 0.5 to 1 ml.

(36) *Injectio Morphinae Sulphatis* (Sterile solution of morphine sulphate in water for injection): sterilised by heating

with a bactericide or by filtration. Dose, $1/8$ to $1/3$ gr. or 8 to 20 mg. subcutaneously.

(37) *Injectio Neoarsphenaminæ* (Sterile solution of the contents of a sealed container of neoarsphenamine in water for injection, prepared immediately before use). Dose of Neoarsphenamine, $2\frac{1}{2}$ to 10 gr. or 0.15 to 0.6 G.

(38) *Injectio Neostigminæ Methylsulphatis* (Sterile solution of neostigmine methylsulphate in water for injection): sterilised by autoclaving or by filtration. Dose of Neostigmine methylsulphate $1/120$ to $1/30$ gr. or 0.5 to 2 mg. subcutaneously or intramuscularly.

(39) *Injectio Nikethamidi* (Nikethamide 25 g., in water for injection 100 ml.): sterilised by filtration or by autoclaving. Dose 15 to 60 min. or 1 to 4 ml. subcutaneously, intramuscularly or intravenously.

(40) *Injectio Œstradiolis Dipropionatis* (Sterile solution of Œstradiol dipropionate in ethyl oleate or a suitable oil); sterilised by heating at 150° for one hour. Dose of Œstradiol dipropionate $1/60$ to $1/12$ gr. or 1 to 5 mg. intramuscularly daily.

(41) *Injectio Œstradiolis Monobenzoatis* (Sterile solution of Œstradiol monobenzoate in ethyl oleate or a suitable oil): sterilised by heating at 150° for one hour. Dose of Œstradiol Monobenzoate $1/60$ to $1/12$ gr. or 1 to 5 mg. intramuscularly daily.

(42) *Injectio Olei Hydnocarpi* (Hydnocarpus oil sterilised by heating at 150° for one hour). Dose, 30 min. increased gradually to 75 min. or 2 ml. to 5 ml. intramuscularly or subcutaneously.

(43) *Injectio Olei Hydnocarpi Œthylici* (Ethyl esters of hydnocarpus oil sterilised by heating at 150° for one hour). Dose, 30 min. gradually increased to 75 min. or 2 ml. to 5 ml. intramuscularly or subcutaneously.

(44) *Injectio Ouabaini* (Sterile solution of ouabain in water for injection): sterilised by autoclaving or by filtration. Dose of Ouabain $1/500$ to $1/240$ gr. or 0.12 to 0.25 mg. intravenously.

(45) *Injectio Oxytocini* (Sterile aqueous solution of the oxytocic principle from the mammalian posterior pituitary) sterilised by filtration or by autoclaving. Has 10 units per ml. Dose, 8 to 15 min. or 0.5 to 1 ml. (5 to 10 units).

(46) *Injectio Penicillini* (Sterile solution of sodium or calcium penicillin in water for injection: freshly prepared by dissolving the contents of a sealed container or requisite number of sterile tablets with aseptic precautions). Each ml. contains 50,000 units. Dose is determined by the physician.

(47) *Injectio Penicillini Oleosa* (Calcium penicillin, sufficient quantity, in white beeswax 4.5 g. and arachis oil to 100 ml.): base is sterilised by heating at 150° for one hour and penicillin added when cool. Each ml. contains 125,000 units.

(48) *Injectio Pethidinæ Hydrochloridi* (Sterile solution of pethidine hydrochloride in water for injection): sterilised by

autoclaving or by filtration. Dose, $2\frac{1}{5}$ to $1\frac{1}{2}$ gr. or 25 to 100 mg. subcutaneously.

(49) *Injectio Phenobarbitoni Sodii* (Sterile solution of the contents of a sealed container of sodium phenobarbitone in water for injection free from CO_2 prepared immediately). Dose of sodium phenobarbitone, 1 to 3 gr. or 60 to 200 mg. intravenously or intramuscularly.

(50) *Injectio Physostigminæ Salicylatis* (Sterile solution of physostigmine salicylate in water for injection containing 0.05% sodium metabisulphite): sterilised by heating with a bactericide or by filtration. Dose of physostigmine salicylate, $1/100$ to $1/50$ gr. or 0.6 to 1.2 mg. subcutaneously.

(51) *Injectio Picrotoxini* (Sterile solution of picrotoxin in water for injection): sterilised by autoclaving or by filtration. Dose of picrotoxin, $1/100$ to $1/20$ gr. or 0.6 to 3 mg. by intravenous or intramuscular injection.

(52) *Injectio Pituitarii Posterioris* (A sterile aqueous extract of the posterior lobe of the pituitary bodies of oxen or other mammals, containing 10 units of oxytocic factor per ml.). Dose, 2 to 5 units (3 to 8 min. or 0.2 to 0.5 ml.) subcutaneously or intramuscularly.

(53) *Injectio Procainæ et Adrenalinæ Fortis* (Procaine hydrochloride 2 g., sodium chloride 0.5 g., chlorocresol 0.1 g., adrenaline chloride solution 2 ml., sodium metabisulphite 0.1 g. and water for injection to 100 ml.): sterilised by heating to 98° to 100° for 30 minutes.

(54) *Injectio Procainæ et Adrenalinæ Mitis* (Procaine hydrochlor. 5 g., sodium chloride 2 g., chlorocresol 0.25 g., and water for injection to 250 ml.): to this are added injection of sodium chloride 750 ml. and injection of adrenaline 2 ml. immediately before use): sterilised by heating to 98° to 100° for 30 minutes.

(55) *Injectio Progesteroni* (Sterile solution of progesterone in ethyl oleate or a suitable oil): sterilised by heating at 150° for one hour. Dose of progesterone by intramuscular injection $1/30$ to $1/3$ gr. or 2 to 20 mg. daily.

(56) *Injectio Quininæ Dihydrochloridi* (Sterile solution of quinine dihydrochloride in water for injection). The solution is sterilised by autoclaving or by filtration. Dose of quinine dihydrochloride, 5 to 10 gr. or 0.3 to 0.6 G.

(57) *Injectio Quininæ et Urethani* (Quinine hydrochloride 12.5 g., urethane 6.25 g. and water for injection to 100 ml.). Dose, 8 to 75 min. or 0.5 to 5 ml. intravenously as a sclerosing agent.

(58) *Injectio Sodii Aurothiomalatis* (Sterile solution of sodium aurothiomalate in water for injection). Sterilised by heating with a bactericide or by filtration. Dose of sodium aurothiomalate, $1/6$ gr. increased to $1\frac{1}{2}$ gr. or 10 mg. increased to 100 mg. intramuscularly weekly.

(59) *Injectio Sodii Bicarbonatis* (Sterile solution of sodium bicarbonate in water for injection : sterilised by autoclaving or by filtration. strength usually 5%) and dose as required.

(60) *Injectio Sodii Chloridi* (Sodium chloride 9 g. and water for injection 1000 ml.). Sterilised by autoclaving or by filtration.

(61) *Injectio Sodii Chloridi Composita* (Sodium chloride 8.6 g., potassium chloride 0.3 g., hydrated calcium chloride 0.48 g. and water for injection to 1000 ml.). Sterilised by autoclaving or by filtration.

(62) *Injectio Sodii Citratis Anticoagulans* (Sodium citrate 25 g., sodium chloride 9 g. and water for injection to 1000 ml.). Sterilised by autoclaving or by filtration.

(63) *Injectio Sodii Citratis cum Dextroso* (Sodium citrate 30 g., dextrose 30 g. and water for injection to 1000 ml. : sodium citrate and dextrose solutions may be prepared separately and mixed in required proportion immediately before use.

(64) *Injectio Sodii Lactatis Compositus*, Hartmann's solution or Ringer-Lactate solution, (Lactic acid 2.4 ml., sodium hydroxide a sufficient quantity, sodium chloride 6 g., potassium chloride 0.4 g., hydrated calcium chloride 0.4 g. and water for injection to 1000 ml.). Sterilised by autoclaving or by filtration.

(65) *Injectio Stibopheni*, (Stibophen 6.4 g., sodium metabisulphite 0.1 g. and water for injection to 100 ml. : reaction adjusted by dilute hydrochloric acid or potassium hydroxide solution to pH 7.0) : sterilised by autoclaving. Dose, 25 to 75 min. or 1.5 to 5 ml.

(66) *Injectio Strychninæ Hydrochloridi* (Sterile solution of strychnine hydrochloride in water for injection). Sterilised by autoclaving or by filtration. Dose of strychnine hydrochloride, 1/30 to 1/16 gr. or 2 to 4 mg. subcutaneously.

(67) *Injectio Sulphadiazinæ Sodii* (Sterile solution of sodium sulphadiazine in water for injection free from CO₂) : sterilised by autoclaving. Dose of Sodium sulphadiazine, 8 to 30 gr. or 0.5 to 2 G. intravenously.

(68) *Injectio Sulpharsphenaminæ* (Sterile solution of sulpharsphenamine from a sealed container in water for injection prepared immediately before use). Dose of sulpharsphenamine, 1½ to 10 gr. or 0.1 to 0.6 G. subcutaneously or intravenously.

(69) *Injectio Sulphathiazoli Sodii* (Sterile solution of sodium sulphathiazole in water for injection) : sterilised by autoclaving. Dose, 8 to 30 gr. or 0.5 to 2 G.

(70) *Injectio Suramini* (Sterile solution of suramin from a sealed container in water for injection prepared immediately before use). Dose of suramin 15 to 30 gr. or 1 to 2 G. intravenously.

(71) *Injectio Testosteroni Propionatis* (Sterile solution of testosterone propionate in ethyl oleate or a suitable oil) : sterilised by heating to 150° for 1 hour. Dose of Testosterone propionate 1/12 to 2/5 gr. or 5 to 25 mg. daily intramuscularly.

(72) *Injectio Theophyllinæ cum Æthylenediamina* (Sterile solution of theophylline with ethylenediamine in water for injection free from CO₂ : sterilised by autoclaving or by filtration. Dose of Theophylline with Ethylenediamine, 1½ to 8 gr. or 0·1 to 0·5 G. intravenously or intramuscularly.

(73) *Injectio Thiopentoni Sodii* (Sterile solution of sodium thiopentone from a sealed container in water for injection, prepared immediately before use). Dose of Sodium thiopentone, 1½ to 8 gr. or 0·1 to 0·5 G. intravenously.

(74) *Injectio Tryparsamidi* (Sterile solution of tryparsamide from a sealed container in water for injection ; prepared immediately before use). Dose, 15 to 30 gr. or 1 to 2 G. subcutaneously, intramuscularly or intravenously.

(75) *Injectio Vasopressini* (Aqueous solution of the pressor and antidiuretic principles from the posterior pituitary). Sterilised by filtration or by autoclaving. Has 10 units per ml. Dose, 8 to 25 min. or 0·5 to 1·5 ml. subcutaneously or intramuscularly.

16. *Lamellæ*, 4.—These discs are made with gelatin 18 g., glycerin 2 g. and distilled water 88 g. or sufficient quantity, for dropping into the eye.

Lamellæ Atropinæ (1/5000 gr. or 0·013 mg. of atropine sulphate) : *Homatrophinæ* (1/100 gr. or 0·65 mg. of homatropine hydrobromide) : *Cocainæ* (1/50 gr. or 1·3 mg. of cocaine hydrochloride) and *Physostigminæ* (1/1000 gr. or 0·065 mg. of physostigmine salicylate).

17. *Linimenta*, 6—These contain anodyne, rubefacient, soothing or stimulating substances and are applied externally and are meant to be rubbed in, except *Linimentum Aconiti* which on account of its toxicity, is simply painted. Alcohol may be replaced by industrial methylated spirit of the same strength and olive oil by arachis, cotton-seed or sesame oil.

(1) *Linimentum Aconiti* (Aconite 500 g., camphor 30 g. and alcohol 90% to 1000 ml.).

(2) *Linimentum Belladonnæ* (Belladonna root percolated with 80% alcohol and camphor added to make 0·375% w/v of alkaloids and 5% w/v of camphor).

(3) *Linimentum Camphoræ* (Camphor 200 g. and arachis oil 800 g.).

(4) *Linimentum Camphoræ Ammoniatum* (Camphor 125 g., oil of lavender 5 ml., strong sol. of ammonia 250 ml. and alcohol 90% to 1000 ml.).

(5) *Linimentum Saponis* (Soft soap 80 g., camphor 40 g., oil of rosemary 15 ml., distilled water 170 ml. and alcohol 90% to 1000 ml.).

(6) *Linimentum Terebinthinæ* (Turpentine oil 650 ml., soft soap 75 g., camphor 50 g. and distilled water to 1000 ml.).

18. *Liquores*, 28—These are simple solutions of various drugs mostly made with distilled water and a few with weak alcohol.

(1) *Liquor Adrenalinæ Hydrochloridi* (Adrenaline 1 g., chlorbutol 5 g., sodium chloride 9 g., sodium metabisulphite 0.5 g., dilute hydrochloric acid 3 ml. and distilled water to 1000 ml.).

(2) *Liquor Ammoniac Dilutus* (Strong sol. of ammonia 333 ml. and distilled water to 1000 ml. : 10% w/w of NH_3).

(3) *Liquor Ammoniac Fortis* (Ammonia is dissolved in water to contain 32.5% w/w of NH_3).

(4) *Liquor Ammonii Acetatis Dilutus* (Strong solution of ammonium acetate 125 ml. and distilled water to 1000 ml. : 7.2% w/v of $\text{C}_2\text{H}_7\text{O}_2\text{N}$) Dose, $\frac{1}{4}$ to 1 fl. oz. or 8 to 30 ml.

(5) *Liquor Ammonii Acetatis Fortis* (Glacial acetic acid 453 g., ammon. bicarb. 470 g., strong sol. of ammonia 100 ml. or q.s. and distilled water to 1000 ml. : 57.5% w/v of $\text{C}_2\text{H}_7\text{O}_2\text{N}$). Dose, 15 to 60 min. or 1 to 4 ml.).

(6) *Liquor Arsenicalis* (Arsenic trioxide 10 g., pot. hydrox. sol. 100 ml., dilute hydrochloric acid 28 ml. or q.s. and distilled water to 1000 ml.) : 1% w/v of As_2O_3). Dose, 2 to 8 min. or 0.12 to 0.5 ml.

(7) *Liquor Calciferolis* (A solution of calciferol in a suitable vegetable oil containing in 1 g. 3000 units of antirachitic activity, vitamin D). Dose, 5 to 20 min. or 0.3 to 1.2 ml. (1000 to 4000 units) daily prophylactic : 10 to 100 min. or 0.6 to 6 ml. (2000 to 20,000 units) daily therapeutic.

(8) *Liquor Calcii Hydroxidi* (Calc. hydrox. 10 g. and distilled water 1000 ml. : 0.15% w/v of $\text{Ca}(\text{OH})_2$). Dose, 1 to 4 fl. oz. or 30 to 120 ml.

(9) *Liquor Chloroxylenolis*, Roxenol, (Chloroxylenol 50 g., terpineol 100 ml., alcohol 95% 200 ml., ricinoleic acid 50 g., pot. hydrox. sol. q.s. and distilled water to 1000 ml.).

(10) *Liquor Cresolis Saponatus*, Lysol, (Cresol 500 ml., linseed oil 180 g., pot. hydroxide 42 g. and distilled water to 1000 ml.)

(11) *Liquor Ferri Perchloridi* (Aqueous solution of ferric chloride containing 15% w/v of it). Dose, 5 to 15 min. or 0.3 to 1 ml.

(12) *Liquor Formaldehydi*, Formalin (Aqueous sol. of formaldehyde containing between 37 to 41% w/v of CH_2O).

(13) *Liquor Hydrargyri Perchloridi* (Mercuric chloride 1 g. and distilled water to 1000 ml. Has 0.1% w/v of mercuric chloride). Dose, 30 to 60 min. or 2 to 4 ml.

(14) *Liquor Hydrogenii Peroxidi* (Hydrogen peroxide is dissolved in water containing 5 to 7% of it, H_2O_2).

(15) *Liquor Iodi Aquosus* (Iodine 50 g., pot. iod. 100 g. and distilled water to 1000 ml.). Dose, 5 to 15 min. or 0.3 to 1 ml.

(16) *Liquor Iodi Fortis* (Iodine 100 g., Pot. iod. 60 g., distilled water 100 ml. and alcohol 90% to 1000 ml.).

(17) *Liquor Iodi Mitis* (Iodine 25 g., potassium iodide 25 g., distilled water 25 ml. and alcohol 90% to 1000 ml. : contains 2.5% w/v of iodine). Dose, 5 to 30 min. or 0.3 to 2 ml.

(18) *Liquor Magnesii Bicarbonatis* (Freshly precipitated mag. carb. in water is saturated with carbon dioxide under 3 atmospheres' pressure): contains 2.5% w/v of mag. bicarb., $\text{Mg}(\text{HCO}_3)_2$. Dose, 1 to 2 fl. oz. or 30 to 60 ml.

(19) *Liquor Morphine Hydrochloridi* (Morphine hydrochloride 10 g., dilute hydrochloric acid 20 ml., alcohol 90% 250 ml. and distilled water to 1000 ml.). Contains 0.76% w/v of anhydrous morphine. Dose, 5 to 30 min. or 0.3 to 2 ml.

(20) *Liquor Picis Carbonis* (Coal tar prepared 200 g., quillaia 100 g. and alcohol 90% to 1000 ml.).

(21) *Liquor Plumbi Subacetatis Fortis* (Lead acetate 250 g., lead monoxide 175 g. and distilled water to 1000 ml.): contains between 19 to 21.5% w/w of total lead.

(22) *Liquor Plumbi Subacetatis Dilutus* (Strong sol. of lead subacetate 12.5 ml. and distilled water to 1000 ml.).

(23) *Liquor Potassii Hydroxidi* (Aqueous sol. of pot. hydrox. containing 5% w/v of it, KOH).

(24) *Liquor Sodæ Chlorinatæ Chirurgicæ*, Dakin's solution (chlorinated lime 18.8 g., sodium carbonate 37.6 g. and boric acid 4 g. or a sufficient quantity and distilled water to 1000 ml.), containing between 0.5 to 0.55% of available chlorine.

(25) *Liquor Strychninæ Hydrochloridi* (Strychnine hydrochloride 10 g., alcohol 90% 250 ml. and distilled water to 1000 ml.). Strychnine hydrochloride content is 0.82% w/v. Dose, 3 to 12 min. or 0.2 to 0.8 ml.

(26) *Liquor Vitamini A Concentratus* (An oily solution containing in 1 g. 50,000 units of vitamin A). Dose, 1 to 10 min. or 0.06 to 0.6 ml., approx. 2500 to 25,000 units, daily.

(27) *Liquor Vitaminorum A et D Concentratus* (An oily solution of vitamins A and D containing in 1 g. 50,000 units of vitamin A and 5000 units of vitamin D). Dose, 1 to 10 min. or 0.06 to 0.6 ml. (Approx. 2500 to 25,000 units of vitamin A and 250 to 2500 units of vitamin D) daily.

(28) *Liquor Vitamini D Concentratus* (An oily solution containing in 1 g. 10,000 units of antirachitic activity vitamin D). Dose, 1½ to 6 min or 0.1 to 0.4 ml. (1000 to 4000 units) daily, prophylactic. 3 to 30 min. or 0.2 to 2 ml. (200 to 20,000 units) daily, therapeutic.

DOSE SCHEDULE.—The following 15 are given orally in doses, 1 to 10 min (Liq. vitamin A, vitamin A and D): 1.5 to 6 min. and 3 to 30 min. (vitamin D) 2 to 8 min. (Liq. Arsen.): 3 to 12 min. (Liq. Strych. Hydrochlor.): 5 to 15 min. (Liq. Ferr. Perchlor. and Iodi Aquosus.): 5 to 30 min. and 10 to 100: min. (Liq. Calciferol.): 5 to 30 min. (Liq. Iol. Mit. and Morph. Hydrochlor.): 15 to 60 min. (Liq. Ammon. Acet. Fort.): 30 to 60 min. (Liq. Hydrarg. Perchlor.): ¼ to 1 fl. oz. (Liq. Ammon. Acet. Dil.): 1 to 2 fl. oz. (Liq. Mag. Bicarb.) and 1 to 4 fl. oz. (Liq. Calc. Hydrox).

19. *Lotio*, 1.—This is a watery solution for applying on wound surfaces.

Lotio Calaminæ (Calamine 150 g., zinc oxide 50 g., glycerin 50 ml. and distilled water to 1000 ml.).

20. **Mella, 3.**—These are preparations of honey and two of these contain acetic acid also and are called oxymella.

Mel Depuratum, Purified honey : *Oxymel* (Acetic acid 150 ml., distilled water 150 ml. and purified honey to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml. : *Oxymel Scillæ* (Squill 50 g., acetic acid 90 ml., distilled water 250 ml. and purified honey sufficient quantity). Dose, 30 to 60 min. or 2 to 4 ml.

21. **Misturæ, 2.**—Here different substances are made into a liquid preparation in which these are either dissolved or suspended.

These are (1) *Misturæ Magnesii Hydroxidi* (Magnesium sulphate 47.5 g., sodium hydroxide 15 g., light magnesium oxide 52.5 g. and distilled water to 1000 ml.). Dose, 60 to 240 min. or 4 to 16 ml. and (2) *Mistura Sennæ Composita*, Black Draught (Magnesium sulphate 25 g., liq. ext. of liquorice 50 ml., compound tinct. of cardamom 100 ml., aromatic spirit of ammonia 50 ml. and infusion of senna to 1000 ml.). Dose, 1 to 2 fl. oz. or 30 to 60 ml.

22. **Mucilagines, 2.**—These are watery solutions or partial solutions of gums, meant to suspend insoluble substances.

(1) *Mucilago Acaciæ* (Acacia 400 g. and chloroform water 600 ml.) and (2) *Mucilago Tragacanthæ* (Tragacanth 12.5 g., alcohol 90% 25 ml. and chloroform water to 1000 ml.).

23. **Oculenta, 7.**—These are ointments for the eye having the basis of 90% of yellow soft paraffin and 10% of wool fat by weight, sterilised by heating at 150° for one hour : prepared with aseptic technique and should be kept in a closed container away from light.

Oculenta Atropinæ (0.25% of atropine sulphate) : *Atropinæ* (0.125% of atropine sulphate) *cum Hydrargyri Oxido* (1% of yellow mercuric oxide), : *Cocainæ* (0.25% of cocaine hydrochloride) : *Hydrargyri Oxidi* (yellow mercuric oxide 1%) : *Hyoscinæ* (hyoschine hydrobromide 0.125%) : *Penicillini* (1000 units of calcium salt per g. and *Physostigminæ* (physostigmine salicylate 0.125%).

24. **Olea 30.**—These are divided into two well marked groups, *fixed* and *volatile* oils. The former are obtained by expression or by boiling with water various vegetable and animal products and skimming of the melted oil. The latter are all obtained by distillation except oil of lemon which is obtained by expression. See p. 29.

Olei Anethi, Anisi, Cajuputi, Cari, Caryophylli, Cinnamomi, Coriandri, Eucalypti, Menthæ Piperitæ, Myristicæ, Rosmarini. Dose, 1 to 3 min. or 0.06 to 0.2 ml. : *Oleum Terebinthinæ*, Dose, 3 to 10 min. or 0.2 to 0.6 ml.

Oleum Hippoglossi, Dose, 1 to 8 min. or 0.06 to 0.5 ml. (vitamin A 1500 to 12,000 units) daily.

Oleum Chenopodii, Dose, 3 to 15 min. or 0.2 to 1 ml.

Olei Hydnocarpi and *Hydnocarpi Athylicum*, Dose, 5 to 15 min. or 0.3 to 1 ml. increased to 60 min. or 4 ml. orally. By injection, 30 min. increased to 75 min. or 2 ml. to 5 ml.

Olei Morrhuæ, DOSE, 60 to 180 min. or 4 to 12 ml. daily in divided doses. *Ricini*, DOSE, 60 to 240 min. or 4 to 16 ml.

Olei Amygdalæ and *Olivæ*, DOSE, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

Olei Amygdalæ Vol. Purificatum, *Arachis*, *Cadinum*, *Gossypii Seminis*, *Lini*, *Iodisatum*, *Lavandulæ*, *Limonis*, *Sesami* and *Theobromatis*, no prescribed dose.

25. *Pasta* 1, A paste is like an ointment and is applied externally.

Pasta Zinci Oxidi Composita (Zinc oxide 250 g., starch 250 g. both finely sifted and white soft paraffin 500 g.).

26. *Pilulæ*, 5.—These are soft solid masses made into little spherical bodies and are intended to be swallowed as a whole. The solid ingredients are first broken up, made into a paste in a mortar with a suitable excipient and then divided in a machine and shaped into pills. Seasonal variations tend to alter their consistency. So these should not be stocked for a long time.

The commercial pills are, however coated and these keep well fairly long. The usual weight of a pill is 5 grains or less.

Four of these are purgatives : (i) *Pilula Aloes* (Aloes 58 g., hard soap 29 g., oil of caraway 3 ml. and syrup of liquid glucose 10 g. or q.s.)

(ii) *Pilula Colocynthis et Hyoscyami* (Colocynth 12.5 g., aloes 25 g., ipomœa resin 25 g., curd soap 7 g., oil of clove 4 ml., dry ext. of hyoscyamus 12.5 g. and syrup of liq. glucose 14 or q.s.).

(iii) *Pilula Hydrargyri*, Blue Pill. (Mercury 33 g., syrup 14 g., liquid glucose 15 g., glycerin 5 g., and liquorice 33 g.).

(iv) *Pilula Rhei Composita* (Rhubarb 25 g., aloes 20 g., hard soap 14 g., all in fine powder, myrrh 14 g., oil of peppermint 2 ml. and syrup of liquid glucose 25 g. or q. s.). DOSE, of each is 4 to 8 gr. or 0.25 to 0.5 G.

The other pill is : (v) *Pilula Ferri Carbonatis* (Exsicc. ferr. sulph. 34 g., exsicc. sod. carb. 21.6 g., tragacanth 2 g., acacia 8.4 g., liquid glucose 32 g. and distilled water 2 ml.). DOSE, 5 to 30 gr. or 0.3 to 2 G.

Most of the pills are distinguishable by the peculiar smell of the volatile oil they contain. Mercury pill is blue and others are blackish brown or black.

27. *Praeparata* 8, are finely prepared powdered vegetable drugs for oral administration.

(i) *Belladonnæ Præparata* (DOSE, $\frac{1}{2}$ to 3 gr. or 30 to 200 mg.).

(ii) *Digitalis Præparata* (DOSE, $\frac{1}{2}$ to 1½ gr. or 30 to 100 mg.).

(iii) *Ergota Præparata* (DOSE, 2½ to 8 gr. or 0.15 to 0.5 g.).

(iv) *Ipecacuanha Præparata* (DOSE, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. and as emetic, 15 to 30 gr. or 1 to 2 G.).

(v) *Nux Vomica Præparata* (DOSE, 1 to 4 gr. or 60 to 250 mg.).

(vi) *Opium Pulveratum* (DOSE, $\frac{1}{2}$ to 3 gr. or 30 to 200 mg.). Two other

preparations from other sources are (vii) *Pix Carbonis Præparata* and (viii) *Styrax Præparatus*.

28. Pulverata, 44.—Certain vegetable drugs are finely pulverised and used only for making various pharmacopœial preparations.

Acaciæ Pulvis, *Aconiti*, *Agar*, *Aloes*, *Anethi*, *Belladonnæ Herbæ*, *Belladonnæ Radicis*, *Calumbæ*, *Capsici*, *Cari*, *Caryophylli*, *Cascaræ Sagradæ*, *Catechu*, *Cinnamomi*, *Colchici Cormi*, *Colchici Seminis*, *Colocynthis*, *Coriandri*, *Digitalis Folii*, *Filicis*, *Fœniculi*, *Gentianæ*, *Glycyrrhizæ*, *Hamamelis*, *Hyoscyami*, *Ipecacuanhæ*, *Ipomœæ*, *Kramerizæ*, *Myristicæ*, *Nucis Vomica*, *Podophylli*, *Podophylli Indici*, *Pruni Serotina*, *Quassia*, *Quillaia*, *Rhei*, *Scillæ*, *Senegæ*, *Sennæ Folii*, *Stramonii*, *Strophanthi*, *Tragacanthæ*, *Valerianæ* and *Zingiberis Pulvis* : also *Saponis duri pulvis*.

29. Pulveres, 7.—Several finely powdered drugs are thoroughly mixed together ; Compound powders.

(1) *Pulvis Cretæ Aromaticus* (Chalk 250 g., cinnamon 100 g., nutmeg 80 g., clove 40 g., cardamom 30 g. and sucrose 500 g. all finely powdered). DOSE, 10 to 60 gr. or 0·6 to 4 G.

(2) *Pulvis Cretæ Aromaticus cum Opio* (Aromatic powder of chalk 975 g. and powdered opium 25 g.). DOSE, 10 to 60 gr. or 0·6 to 4 G.

(3) *Pulvis Effervescens Compositus* (No. 1. Sod. pot. tart. 7·5 g. and sod. bicarb. 2·5 g. in blue paper : No. 2. Tartaric acid 2·5 g. in white paper ; to be taken mixed while effervescing in water).

(4) *Pulvis Glycyrrhizæ Compositus* (Senna leaf 160 g., liquorice 160 g., fennel 80 g., sublimed sulphur 80 g. and sucrose 520 g. all finely powdered). DOSE, 60 to 120 gr. or 4 to 8 G.

(5) *Pulvis Ipecacuanhæ et Opii* (Ipecacuanha 100 g., opium 100 g. and lactose 800 g.). DOSE, 5 to 10 gr. or 0·3 to 0·6 G.

(6) *Pulvis Rhei Compositus* (Rhubarb 250 g., ginger 100 g., both finely powdered, heavy and light mag. carb. each 325 g.). DOSE, 10 to 60 gr. or 0·6 to 4 G.

(7) *Pulvis Tragacanthæ Compositus* (Tragacanth 150 g., acacia 200 g., starch 200 g. and sucrose 450 g. all finely powdered). DOSE, 10 to 60 gr. or 0·6 to 4 G.

DOSE SCHEDULE.—5 to 10 gr. (*Pulv. Ipecac. et Opii*) : 10 to 60 gr. (*Pulv. Cret. Aromat.*, *Cret. Aromat. c Opio*, *Rhei Co.* and *Trag. Co.*) : 60 to 120 gr. (*Pulv. Glycyrrh. Co.*) and the whole quantity, 192·5 gr. (*Pulv. Efferv. Co.*).

30. Sera Antitoxic, 6.—These are prepared by immunising a horse with graduated doses of standardised exotoxin of specific bacteria. When high degree of immunity is reached, the horse is bled, the antitoxic globulin fraction is taken out, dissolved in normal saline and put up for use.

(1) *Antitoxinum Diphthericum* (DOSE, 500 to 2000 units, prophylactic : not less than 10,000 units therapeutic).

(2) *Antitoxinum Œdematiens* (Dose, 10,000 units, prophylactic : not less than 30,000 units therapeutic).

(3) *Antitoxinum Septicum* (Vibrion septicum). Dose, 5000 units prophylactic : not less than 15,000 units therapeutic.

(4) *Antitoxinum Welchicum* (Perfringens), Dose, 10,000 units prophylactic : not less than 30,000 units therapeutic).

(5) *Antitoxinum Œdematiens Compositum* (Mixed gas-gangrene antitoxin). Dose, Antitoxic. œdemat. not less than 10,000 units : antitoxic. septic. not less than 5000 units and welchic (perfringens) not less than 10,000 units, prophylactic. Not less than 3 times of the above, therapeutic.

(6) *Antitoxinum Tetanicum* (Dose, not less than 3000 units prophylactic : not less than 100,000 units therapeutic).

Therapeutic doses of all these may be repeated as required.

31. % **spiritus**, 8. These are either simple, being the solutions of a single substance or complex solutions of various substances in alcohol (90%).

(a) Of volatile oils : The spiritus are prepared by dissolving the substance 100 ml. or g., in alcohol (90%) 1000 ml. These are *Spiritus Cajuputi*, *Camphoræ* and *Mentha Piperita*. Dose, 5 to 30 min. or 0.3 to 2 ml.

(b) Of other substances : (i) *Spiritus Chloroformi* (Chloroform 50 ml. and alcohol 90%, 1000 ml.). Dose, 5 to 30 min. or 0.3 to 2 ml. (ii) *Spiritus Ætheris* (Anæsthetic ether 330 ml. and alcohol 90% to 1000 ml.). Dose, 15 to 60 min. or 1 to 4 ml.

(c) Complex spirits : (i) *Spiritus Ammonia Aromaticus* (Ammon. bicarb. 25 g., strong sol. of ammonia 60 ml., oil of lemon 5 ml., oil of nutmeg 3 ml., alcohol 90%, 750 ml. and distilled water to 1000 ml.). (ii) *Spiritus Ætheris Nitrosi* (Ethyl nitrite 1.25 to 2.5% w/v in alcohol 90%). Dose of both, 15 to 60 min. or 1 to 4 ml.

Spiritus Methylatus Industrialis (Alcohol 95%, 19 volume and wood naphtha 1 volume).

Formerly in this group was *Spiritus Rectificatus* which is obtained by distillation of fermented sugars, but is now grouped under alcohol as alcohol 90%.

32. **Suppositoria**, 10.—These are solid conical bodies containing various active medicines meant to be introduced into the rectum. The approximate weight is 1 gm. and made up with oil of theobroma to which a certain amount of white beeswax may be added in the hot weather to give sufficient solidity (raising the melting point to 37°).

The dose of the active drugs is stated by the prescriber. If not, these will be as follows :

Suppositoria *Acidi Tannici* (3 gr. or 0.2 g.); *Belladonna* (Liq. ext. of belladonna 2.5 min. or 0.15 ml., containing 1/60 gr. or 1 mg. of the total alkaloids.) ; *Bismuthi Subgallatis* (5 gr. or 0.3 g.) ; *Cocainæ* (0.25 gr. or 15 mg. of hydrochloride) ; *Hamamelidis* (dry extract 3 gr. or 0.2 g.) ; *Hamamelidis et Zinc* *Oxidi* (dry extract 3 gr. or 0.2 g. and zinc oxide 10 gr. 0.6 g.) ;

Iodoformi (3 gr. or 0·2 g.) ; *Morphinæ* (hydrochloride 0·25 gr. or 15 mg.) and *Phenolis* (1 gr. or 60 mg.).

Suppositoria Glycerini (gelatin 14 g. and glycerin 70 g. and distilled water q.s.) does not contain oil of theobroma. Children are usually given one of 1 g. size and for older subjects, bigger.

33. *Syrupi*, 10.—These are strong solutions of sugar, containing various active drugs, sugar acting as flavouring and preservative.

(1) *Syrupus* (Sucrose 667 g. and distilled water to 1000 g.).

(2) *Syrupus Aurantii* (Tinct. of orange 125 ml. and syrup to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml.

(3) *Syrupus Ferri Phosphatis Compositus* (Iron 4·3 g., phosphoric acid 48 ml., calc. carb. 13·6 g., pot. bicarb. 1 g., sod. phosph. 1 g., cocuineal 3·5 g., sucrose 700 g., orange flower water of commerce 50 ml. and distilled water to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml., contains 0·9% w/v of ferrous phosphate and 1·4% w/v of tricalcium phosphate). Dose, 30 to 120 min. or 2 to 8 ml.

(4) *Syrupus Glucosi Liquidi* (Liq. glucose 333 g. and syrup 667 g.).

(5) *Syrupus Limonis* (Fresh lemon peel 60 g., alcohol 60% q.s., citric acid 24 g. and syrup to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml.

(6) *Syrupus Pruni Serotinæ* (Wild cherry bark 150 g., sucrose 800 g., glycerin 50 ml. and distilled water to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml.

(7) *Syrupus Scillæ* (Vinegar of squill 450 ml., sucrose 800 g. and distilled water to 1000 ml.). Dose, 30 to 60 min. or 2 to 4 ml.

(8) *Syrupus Sennæ* (Liquid extract of senna 250 ml. and syrup to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml.

(9) *Syrupus Tolutanus* (Balsam of tolu 25 g., sucrose 660 gr. and distilled water to 1000 g.). Dose, 30 to 120 min. or 2 to 8 ml.

(10) *Syrupus Zingiberis* (Strong tincture of ginger 50 ml. and syrup to 1000 ml.). Dose, 30 to 120 min. or 2 to 8 ml.

DOSE SCHEDULE.—30 to 60 min. (Syr. Scill.): 30 to 120 min. (Syr. Aurant., Ferr. Phosph. Co., Limon., Prun. Serot., Senn., Tolu. and Zingib.): No dose (Syr. and Syr. Glucos. Liq.).

34. **Tabellæ**, 49, are flat or biconvex circular discs prepared by compressing a drug or a mixture of drugs with or without excipient by punches in suitable dies. The material may be prepared in a dry granular form suitable for passing through the compressing machine by such processes as moist granulation, dry granulation or granulation by preliminary compression.

Moulded tablets or tablet triturates are flat circular discs prepared by pressing moistened powder with moulds.

(a) **Moist granulation**: the drug or drugs with a diluent, absorbent or an adhesive as lactose, sucrose, dextrose, starch, dextrin, sodium chloride and

powdered acacia, with a moistening agent as distilled water, alcohol, isopropyl-alcohol, mucilage of acacia or of starch, ethereal solution of oil of theobroma or aqueous solution of glucose, sucrose or gelatin is or are made into granules, dried at a temperature not exceeding 60°.

(b) *Dry granulation* : the drug itself during manufacture is in granular form or in crystals. This may be passed through a sieve to obtain required fineness.

(c) *Granulation by preliminary compression* : the material is first compressed into large tablets and then broken up into granules, a disintegrating and a lubricating agents are added before final treatment.

Colouring and flavouring agents are also sometimes added. The weight of the tablets should be uniform.

Label should state the name with quantity of the active ingredients.

Mg. = moist granulation. Dg. = dry granulation. C. = compression,

(1) *Tabellæ Acetomenaphthoni* (Mg. and C.). DOSE of aceto menaphthone, $\frac{1}{30}$ to $\frac{1}{6}$ gr. or 2 to 10 mg. Usually each tablet in 5 mg.

(2) *Tabellæ Acidi Acetylsalicylici* (Dg. and C.). DOSE, 5 to 15 gr. or 0.3 to 1 G. Usually each 5 gr.

(3) *Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio* (Mg. and C. of equal parts of powdered acetylsalicylic acid and ipecacuanha and opium powder). DOSE, 1 to 2 tablets, each of 5 gr. Usually each tablet has $2\frac{1}{2}$ gr. of each of acetyl salicylic acid and ipecac.-opium powder.

(4) *Tabellæ Acidi Acetylsalicylici et Phenacetini* (Acetylsalicylic acid 226.8 g. in Dg. and phenacetin 162 g. in Mg. : finally made up by C.). DOSE, 1 to 2 tablets, each containing acetylsalicylic acid $3\frac{1}{2}$ gr. and phenacetin $2\frac{1}{2}$ gr.

(5) *Tabellæ Acidi Ascorbici* (Mg, drying and C.). DOSE, $\frac{2}{5}$ to $1\frac{1}{4}$ gr. or 25 to 75 mg daily as prophylactic : 3 to 8 gr. or 0.2 to 0.5 G. therapeutic daily. Usually each is 50 mg

(6) *Tabellæ Acidi Nicotinici* (Mg. and C.). DOSE, $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 15 to 30 mg. prophylactic and $\frac{3}{4}$ to 4 gr. or 50 to 250 mg therapeutic daily. Usually each, 50 mg.

(7) *Tabellæ Æthisteroni* (Mg. and C.). DOSE, $\frac{1}{12}$ to 2.5 gr. or 5 to 25 mg. daily. Usually each 5 mg

(8) *Tabellæ Aneurinæ Hydrochloridi* (Mg. and C.). DOSE, prophylactic $\frac{1}{60}$ to $\frac{1}{20}$ gr. or 1 to 3 mg. and therapeutic $\frac{1}{6}$ to $\frac{1}{2}$ gr. or 10 to 30 mg. daily. Usually each, 1 mg,

(9) *Tabellæ Atropinæ Sulphatis* (Mg. and C.). DOSE, $\frac{1}{240}$ to $\frac{1}{60}$ gr. or 0.25 to 1 mg. Usually each $\frac{1}{100}$ gr.

(10) *Tabellæ Barbitoni* (Mg. and C.). DOSE, 5 to 10 gr. or 0.3 to 0.6 G.

(11) *Tabellæ Barbitoni Sodii* (Mg. and C.). DOSE, 5 to 10 gr. or 0.3 to 0.6 G.

(12) *Tabellæ Calcii Lactatis* (Mg. and C.). DOSE, 15 to 60 gr. or 1 to 4 G. Usually each. 5 gr.

(13) *Tabellæ Codeinæ Phosphatis* (Mg. and C.). DOSE, $\frac{1}{6}$ to 1 gr. or 10 to 60 mg. Usually each, $\frac{1}{2}$ gr.

(14) *Tabellæ Codeinæ Compositæ* (Acetylsalicylic acid 259·2 g. in Dg., phenacetin 259·2 g. and codeine phosphate 8·1 g. in Mg. and made up by C. for 1000 tablets. Dose, 1 to 2 tablets, each containing acetylsalicylic acid 4 gr., phenacetin 4 gr. and codeine phosphate $\frac{1}{4}$ gr.

(15) *Tabellæ Dienæstrolis* (Mg. and C.). Dose, 1/600 to 1/12 gr. or 0·1 to 5 mg. Usually each, 0·1 mg.

(16) *Tabellæ Digitalis Præparatæ* (Mg. and C.). Dose, $\frac{1}{2}$ to $1\frac{1}{2}$ gr. or 30 to 100 mg. Usually each, 1 gr.

(17) *Tabellæ Digoxini* (Mg. and C.). Dose, initial 1/60 to 1/40 gr. or 1 to 1·5 mg. : maintenance, 1/240 gr. or 0·25 mg. once or twice daily. Usually each, 0·25 mg.

(18) *Tabellæ Ephedrinæ Hydrochloridi* (Mg. and C.). Dose, $\frac{1}{4}$ to 1 gr. or 16 to 60 mg. Usually each, $\frac{1}{2}$ gr.

(19) *Tabellæ Ergotæ Præparatæ* (Mg. and C.) : not less than 15% of the total alkaloids are water soluble (ergometrine). Dose, $2\frac{1}{2}$ to 8 gr. or 0·15 to 0·5 G. Usually each, $2\frac{1}{2}$ gr.

(20) *Tabellæ Glycerylis Trinitratis* (With chocolate basis by Mg. and C.). Dose, 1/130 to 1/60 gr. or 0·5 to 1 mg. Usually each, 1/130 gr.

(21) *Tabellæ Hexæstrolis* (Mg. and C.). Dose, 1/60 to 1/12 gr. or 1 to 5 mg. daily. Usually each, 1 mg.

(22) *Tabellæ Hydrargyri cum Creta* (Mg. and C. : Hg. 28 to 38·5%). Dose, 1 to 5 gr. or 60 to 300 mg. Usually each, 1 gr.

(63) *Tabellæ Hydrargyri Subchloridi* (Mg. and C.). Dose, $\frac{1}{2}$ to 3 gr. or 30 to 200 mg. Usually each, 1 gr.

(24) *Tabellæ Ipecacuanhæ et Opii* (Mg. and C. : morphine 0·9 to 1·1%). Dose, 5 to 10 gr. or 0·3 to 0·6 G. of Powder of Ipecacuanha and opium. Usually each, 5 gr.

(25) *Tabellæ Mepacrinæ Hydrochloridi* (Mg. and C.). Dose, prophylactic $1\frac{1}{2}$ gr. or 0·1 G. daily : therapeutic 3 to 8 gr. or 0·2 to 0·5 g. daily (in divided doses). Usually each, 0·1 g.

(26) *Tabellæ Methyltestosteroni* (Mg. and C.). Dose, $2\frac{1}{5}$ to $\frac{3}{4}$ gr. or 25 to 50 mg. : in women 1/12 to $\frac{1}{3}$ gr. or 5 to 20 mg. daily. Usually each, 5 mg.

(27) *Tabellæ Methylthiouracili* (Mg. and C.). Dose, $1\frac{1}{2}$ to 3 gr. or 0·1 to 0·2 G. Usually each, 0·1 g.

(28) *Tabellæ Nicotinamidi* (Mg. and C.). Dose, prophylactic $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 15 to 30 mg. and therapeutic $\frac{3}{4}$ to 4 gr. or 50 to 250 mg. daily. Usually each, 50 mg.

(29) *Tabellæ Estroni* (Mg. and C.). Dose, 1/60 to $\frac{1}{6}$ gr. or 1 to 10 mg. daily. Usually each, 1 mg.

(30) *Tabellæ Phenacetini* (Mg. and C.). Dose, 5 to 10 gr. or 0·3 to 0·6 G. Usually each, 5 gr.

(31) *Tabellæ Phenazoni* (Mg. and C.). Dose, 5 to 10 gr. or 0·3 to 0·6 G. Usually each, 5 gr.

(32) *Tabellæ Phenobarbitoni* (Mg. and C.). Dose, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg.

(33) *Tabellæ Phenobarbitoni Sodii* (Mg. and C.). Dose, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg.

(34) *Tabellæ Phenolphthaleini* (with chocolate basis by Mg. and C.). DOSE, 1 to 5 gr. or 60 to 300 mg. Usually each, 2 gr.

(35) *Tabellæ Potassii Bromidi* (Dg. and C.). DOSE, 5 to 20 gr. or 0·3 to 1·2 G. Usually each, 5 gr.

(36) *Tabellæ Potassii Chloratis* (Dg. and C.). DOSE, 5 to 10 gr. or 0·3 to 0·6 G. Usually each, 5 gr.

(37) *Tabellæ Quiniæ Bisulphatis* (Mg. and C.). DOSE, 5 to 10 gr. or 0·3 to 0·6 G. Usually each, 5 gr.

(38) *Tabellæ Quiniæ Hydrochloridi* (Mg. and C.) DOSE, 5 to 10 gr. or 0·3 to 0·6 G. Usually each, 5 gr.

(39) *Tabellæ Sodii Bicarbonatis Compositæ* (Sodium bicarbonate 324 g. and oil of peppermint 4 ml. : make 1000 tablets by Mg. and C.) DOSE, 2 to 6 tablets.

(40) *Tabellæ Sodii Citratis* (Mg. or Dg. and C.). DOSE, 15 to 60 gr. or 1 to 4 G. Usually each, 2 gr.

(41) *Tabellæ Sodii Salicylatis* (Mg. and C.). DOSE, 10 to 30 gr. or 0·6 to 2 G. Usually each, 5 gr.

(42) *Tabellæ Stilbestrolis* (Mg. and C.). DOSE, 1·120 to 1·30 gr. or 0·5 to 2 mg. Usually each, 0·5 mg.

(43) *Tabellæ Succinylsulphathiazoli* (Mg. and C.). DOSE, 45 to 90 gr. or 3 to 6 G.

(44) *Tabellæ Sulphadiazinæ* (Mg. and C.). DOSE, initial 30 gr. or 2 G. afterwards 15 gr. or 1 G. every 4 hours.

(45) *Tabellæ Sulphaguanidinæ* (Mg. and C.). DOSE, 30 to 60 gr. or 2 to 4 G.

(46) *Tabellæ Sulphanilamidi* (Mg. and C.). DOSE, initial 30 gr. or 2 G. afterwards 15 gr. or 1 G. every 4 hours.

(47) *Tabellæ Sulphathiazoli* (Mg. and C.). DOSE, initial 30 gr. or 2 G. afterwards 15 gr. or 1 G. every 4 hours.

(48) *Tabellæ Thiouracili* (Mg. and C.). DOSE, 2 to 3 gr. or 0·1 to 0·2 G. Usually each, 0·1 G.

(49) *Tabellæ Thyroidei* (Mg. and C.) : Iodine content 0·08 to 0·12%. DOSE, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. : usually each $\frac{1}{2}$ gr.

34. Tincturæ, 29.—These are alcoholic solutions of active principles of vegetable products, prepared in the following way.

(a) **MACERATION.**—The drug is soaked in the menstruum for seven days and occasionally shaken. It is then strained : the marc is pressed and strained and the two liquids are mixed : an example of this is the preparation of *Tinctura Aurantii* : clarified by subsidence or by filtration.

(b) **PERCOLATION.**—The drug is soaked for four hours and is then put up into the percolator and enough of menstruum is added to leave a layer of it on the top. This is allowed to remain for 24 hours and then slowly percolated. The marc is afterwards pressed and the two liquids are mixed and sufficient menstruum is added to make up the required volume.

(c) **SOLUTION.**—Some are simple solution in alcohol.

M, prepared by maceration. *P*, by percolation. *S*, by solution.

(1) *Tinctura Aurantii* (Fresh bitter orange peel 250 g. and alcohol 90% 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(2) *Tinctura Belladonnæ* (Belladonna herb 100 g. and alcohol 70% sufficient quantity for required strength of 0.03% w/v of total alkaloids). *P.* Dose, 5 to 15 min. or 0.3 to 1 ml.

(3) *Tinctura Benzoini Composita* (Benzoin 100 g., storax 75 g., balsam of tolu 25 g., aloes 20 g. and alcohol 90% to 1000 ml.). *M.*

(4) *Tinctura Calumbæ* (Calumba 100 g. and alcohol 60% 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(5) *Tinctura Capsici* (Capsicum 50 g., alcohol 60% 1000 ml.). *M.* Dose, 5 to 15 min. or 0.3 to 1 ml.

(6) *Tinctura Cardamomi Composita* (Cardamom 14 g., caraway 14 g., cinnamon 28 g., cochineal 7 g., glycerin 50 ml. and alcohol 60% to 1000 ml.). *P.* Dose, 30 to 60 min. or 2 to 4 ml.

(7) *Tinctura Catechu* (Catechu 200 g., cinnamon 50 g. and alcohol 45% 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(8) *Tinctura Cocci* (Cochineal 100 g. and alcohol 45% 1000 ml.). *M.*

(9) *Tinctura Colchici* (Liq. ext. of colchicum 100 ml. and alcohol 60% to 1000 ml.). *S.* Dose, 5 to 15 min. or 0.3 to 1 ml. 15 min. contains 1/200 gr. of colchicine (0.03%).

(10) *Tinctura Digitalis* (Digitalis leaf 100 g. or prepared digitalis 80 g. and alcohol 70% 1000 ml. or q.s.). *P.* or *M.* Dose, 5 to 15 min. or 0.3 to 1 ml. : 15 min. contains 1 unit of activity.

(11) *Tinctura Gentianæ Composita* (Gentian 100 g., dry bitter orange peel 37.5 g., cardamom 12.5 g. and alcohol 45% to make 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(12) *Tinctura Hyoscyami* (Liq. ext. of hyoscyamus 100 ml. and alcohol 70% to 1000 ml.). *S.* Dose, 30 to 60 min. or 2 to 4 ml. : 60 min. contains 1/320 gr. of the alkaloids (0.005%).

(13) *Tinctura Ipecacuanhæ* (Liq. ext. of ipecac. 50 ml., dilute acetic acid 16.5 ml., alcohol 90% 210 ml., glycerin 200 ml. and distilled water to 1000 ml.). *S.* Dose, 10 to 30 min. or 0.6 to 2 ml. and as emetic 1/3 to 1 fl. oz. or 15 to 30 ml. : 30 min. contains 1/30 gr. of total alkaloids (0.1%).

(14) *Tinctura Limonis* (Fresh lemon peel 250 g. and alcohol 60% 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(15) *Tinctura Myrrhæ* (Myrrh 200 g. and alcohol 90% to 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(16) *Tinctura Nucis Vomicae* (Liq. ext. of nux vomica 83.4 ml. and alcohol 45% to 1000 ml.). *S.* Dose, 10 to 30 min. or 0.6 to 2 ml. : 30 min. contains 1/30 gr. (0.125%).

(17) *Tinctura Opii* (Opium 200 g., alcohol 90% and distilled water each 500 ml. or q.s.). *S.* Dose, 5 to 30 min. or 0.3 to 2 ml. : 30 min. contains 1/3 gr. morphine (1%).

(18) *Tinctura Opii Camphorata* (Tincture of opium 50 ml., benzoic acid 5 g., camphor 3 g., oil of anise 3 ml. and alcohol 60% to 1000 ml.) : contains 0.05% of morphine. *S.* Dose, 30 to 60 min. or 2 to 4 ml.

(19) *Tinctura Quassiae* (Quassia 100 g. and alcohol 45% 1000 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(20) *Tinctura Rhei Composita* (Rhubarb 100 g., cardamom 12.5 g., eoriander 12.5 g., glycerin 100 ml. and alcohol 60% to 1000 ml.). *P.* Dose, 30 to 60 min. or 2 to 4 ml.

(21) *Tinctura Scillæ* (Squill 100 g. and alcohol 60% 1000 ml.). *M.* Dose, 5 to 30 min. or 0.3 to 2 ml.

(22) *Tinctura Senegæ* (Liq. ext. of senega 200 ml. and alcohol 60% to 1000 ml.). *S.* Dose, 30 to 60 min. or 2 to 4 ml.

(23) *Tinctura Stramonii* (Liq. ext. of stramonium 100 ml. and alcohol 45% to 1000 ml.). *S.* Dose, 5 to 30 min. or 0.3 to 2 ml., contains 0.025% alkaloids.

(24) *Tinctura Strophanthi* (Strophanthus 100 g. and alcohol 70% 500 ml. or q.s. to produce a tincture of required strength). *P.* Dose, 2 to 5 min. or 0.12 to 0.3 ml.

(25) *Tinctura Tolutana* (Balsam of tolu 100 g. and alcohol 90% to 1000 ml.). *S.* Dose, 30 to 60 min. or 2 to 4 ml.

(26) *Tinctura Valerianæ Ammoniata* (Valerian 200 g., oil of nutmeg 3 ml., oil of lemon 2 ml., dilute ammonia sol. 100 ml. and alcohol 60% to 900 ml.). *M.* Dose, 30 to 60 min. or 2 to 4 ml.

(27) *Tinctura Zingiberis Fortis* (Ginger 500 g. and alcohol 90% 1000 ml.). *P.* Dose, 5 to 10 min. or 0.3 to 0.6 ml.

(28) *Tinctura Zingiberis Mitis* (Strong tincture 200 ml. and alcohol 90% to 1000 ml.). *S.* Dose, 30 to 60 min. or 2 to 4 ml.

DOSE SCHEDULE.—(i) 2 to 5 min. (Tinct. Strophanth.). (ii) 5 to 10 min. (Tinct. Zingib. Fort.). (iii) 5 to 15 min. (Tinct. Bellad., Capsic., Colch. and Digit.). (iv) 5 to 30 min. (Tinct. Opii, Scill. and Stramon.). (v) 10 to 30 min. (Tinct. Ipecac. and Nuc. Vom.). (vi) 30 to 60 min. (Tinct. Aurant., Calumb., Cardam. Co., Catech., Gent. Co., Hyoscy., Limon., Myrrh., Opii Camph., Quass., Rhei Co., Seneg., Tolu., Valerian Ammon. and Zingib. Mit.). (vii) No dose (Tinct. Benzoin. Co. and Cocc.).

35. Toxina, 7.—These are standardised exotoxin of bacteria obtained from sterile filtrate of the culture.

(a) *Toxinum Diphthericum Calefactum* or Schick Control (Schick test toxin is heated to a temperature not less than 70° for not less than 5 minutes). Dose, 3 min. or 0.2 ml. intradermally, diagnostic.

(b) *Toxinum Diphthericum Detoxicatum* or Diphtheria Prophylactic (Sterile filtrate or material derived from the filtrate of a broth culture of *C. diphtheriæ* with reduced toxicity but intact antigenic property. This may be *formol toxoid*, *alum precipitated toxoid*, *toxoid-antitoxin mixture* and *toxoid-antitoxin floccules*. These are called in abbreviation, F.T., A.P.T., T.A.M. and T.A.F. Dose of F.T., as indicated on the label, given on 2 or 3 occasions at not less than 4 weeks' interval in case of two injections and if 3rd injection is given, at not less than 2 weeks' interval : of A.P.T. 0.2 to 0.5 ml. repeated after not less than 4 weeks, 0.5 ml. : of T.A.M. 1 ml. at not less than 4 weeks'

interval (two doses) and after not less than 2 weeks, the 3rd dose : of *T.A.F.* 1 ml. at not less than 4 weeks' interval (two doses) and not less than two weeks' after, the 3rd dose : all by intramuscular injection.

(c) *Toxinum Diphthericum Diagnosticum* (Schick test toxin is sterile filtrate from a mature culture of *C. diphtheriæ*, diluted to contain in 0.2 ml. the test dose for the diagnosis of susceptibility). DOSE, 3 min. or 0.2 ml. intradermally.

(d) *Toxinum Staphylococcicum Detoxicatum* (*Staphylococcus Toxoid* is the sterile filtrate of the culture of a toxigenic strain of *staphylococcus*. DOSE, $\frac{3}{4}$ min. increased to 15 min. or 0.05 ml. increased to 1 ml. intramuscularly.

(e) *Toxinum Tetanicum Detoxicatum* : Tetanus toxoid is the sterile filtrate of a culture of *C. tetani*. The specific toxicity has been removed by chemical means retaining the antigenic properties. This may be in (i) formalin treated *Simple solution* or (ii) as *Alum precipitated toxoid*. DOSE, 8 to 15 min. or 0.5 to 1 ml. subcutaneously or intramuscularly and after an interval of not less than 6 weeks, a second dose of 15 min. (1 ml.).

(f) *Tuberculinum Pristinum*, Old tuberculin, a concentrated filtrate from a fluid culture medium in which *M. tuberculosis* has been grown. DOSE, 1/6000 to 1/60 min. or 0.00001 to 0.001 ml. intradermally, diagnostic. Strength, as of the standard preparation.

(g) *Tuberculini Derivativum Proteinicum Purificatum*, purified protein derivative of tuberculin or P.P.D. is precipitated tuberculin of potency equivalent to that of standard old tuberculin. DOSE, 0.1 ml., each ml. containing potency of 0.0001 ml., 0.001 ml. or 0.01 ml. of the standard old tuberculin.

36. **Trochisci**, 7.—These are small tablets (lozenges), meant to be sucked in the mouth.

For 1000 lozenges, sugar (1000 g.), gum acacia (70 g.), tincture of tolu (20 ml.) and distilled water with 1000 times of quantity of the active substances are made into a paste, divided into 1000 lozenges and dried in a hot chamber at a moderate temperature.

Trochisci Acidi Tannici (has tannic acid $\frac{1}{2}$ gr. or 30 mg.) ; *Bismuthi Co.* (bismuth carbonate and heavy mag. carbonate each 150 g., calcium carbonate 300 g., acacia 70 g., sucrose 1000 g., oil of rose 0.05 ml. and distilled water q.s. for 1000, each containing bismuth carbonate $2\frac{1}{2}$ grs.) ; *Krameriæ* (has dry extract 1 gr.) : *Krameriæ et Cocainæ* (1 gr. of dry extract and $\frac{1}{20}$ gr. of cocaine hydrochloride) : *Morphinæ et Ipecacuanhæ* ($\frac{1}{32}$ gr. of morphine hydrochloride and $\frac{1}{10}$ gr. of prepared ipecac.) : *Phenolis* (Phenol liquid 35.5 ml., acacia 90 g., tragacanth 30 g., citric acid 7 g., carmine 3 g., sucrose 1000 g. and distilled water q.s. for 1000 : $\frac{1}{2}$ gr. phenol in each) and *Trochisci Penicillini* (500 units in 1 g.).

37. **Unguenta**, 25.—These are mixtures for external application only, made into semisolid preparations with lard, olive

oil, beeswax, emulsifying wax, paraffin, wool alcohols or with hydrous wool fat.

Lard may turn rancid and is therefore mixed with benzoic acid. If the medicine is meant to be absorbed through the skin, either lard, suet, wool alcohols or hydrous wool fat should be the basis. For a wound surface, paraffin is the best. If in hot climate the basis become too soft, a certain amount of lard, suet or beeswax may be added.

(1) *Unguentum Acidi Borici* (Boric acid 10 g. and paraffin ointment 990 g.).

(2) *Unguentum Acidi Salicylici* (Salicylic acid 20 g. and ointment of wool alcohols 980 g.).

(3) *Unguentum Alcoholium Lanæ* (Wool alcohols 60 g., hard paraffin 240 g., white or yellow soft paraffin 100 g. and liquid paraffin 600 g.).

(4) *Unguentum Aquosum* (Ointment of wool alcohols 500 g. and distilled water 500 ml.).

(5) *Unguentum Capsici* (Capsicum 250 g. and simple ointment 950 g.).

(6) *Unguentum Dithranolis* (Dithranol 1 g. and yellow soft paraffin 999 g.).

(7) *Unguentum Emulsificans* (Emulsifying wax 300 g., white soft paraffin 500 g. and liquid paraffin 200 g.).

(8) *Unguentum Emulsificans Aquosum* (Emulsifying ointment 300 g., chlorocresol 1 g. and distilled water 699 g.).

(9) *Unguentum Hamamelidis* (Liquid extract of hamamelis 10 ml., wool fat 50 g. and yellow soft paraffin 40 g.).

(10) *Unguentum Hydrargyri* (Mercury 300 g., oleated mercury 15 g., wool fat 430 g., white beeswax 70 g. and white soft paraffin 185 g.).

(11) *Unguentum Hydrargyri Ammoniaci* (Ammoniated mercury 25 g. and simple ointment 975 g.).

(12) *Unguentum Hydrargyri Compositum* (Ointment of mercury 400 g., yellow beeswax 240 g., olive oil 240 g. and camphor 120 g.).

(13) *Unguentum Hydrargyri Dilutum* (Ointment of mercury 333.3 g. and simple ointment 666.7 g.).

(14) *Unguentum Hydrargyri Nitratis Dilutum* (Strong ointment of mercuric nitrate 200 g. and yellow soft paraffin 800 g.).

(15) *Unguentum Hydrargyri Nitratis Forte* (Mercury 10 g., nitric acid 30 ml., lard 40 g. and olive oil 70 g.).

(16) *Unguentum Hydrargyri Oleati* (Oleated mercury 250 g. and hydrous ointment 750 g.).

(17) *Unguentum Hydrargyri Subchloridi* (Mercurous chloride 200 g. and hydrous ointment 800 g.).

(18) *Unguentum Paraffini* (White beeswax 20 g., hard paraffin 80 g. and white or yellow soft paraffin 900 g.).

(19) *Unguentum Penicillini* (Calcium penicillin quantity as required and ointment of wool alcohols 100 g.): strength usually 500 units per g.

(20) *Unguentum Phenolis* (Phenol 30 g., white beeswax 75 g., lard 50 g., hard paraffin 75 g. and white soft paraffin 770 g.).

(21) *Unguentum Simplex* (Wool fat 50 g., hard paraffin 100 g. and white or yellow soft paraffin 850 g.).

(22) *Unguentum Sulphuris* (Sublimed sulphur 100 g. and simple ointment of white soft paraffin 900 g.).

(23) *Unguentum Zinci Oleatis* (Zinc sulphate 30 g., hard soap shavings 90 g., boiling distilled water and white soft paraffin each a sufficient quantity having 5.2% of ZnO).

(24) *Unguentum Zinci Oxidi* (Zinc oxide 150 g. and simple ointment 850 g., having ZnO 15%).

(25) *Unguentum Zinci Oxidi Aquosum* (Zinc oxide 150 g. and hydrous ointment 850 g.).

38. *Vaccina*, 7 + 3.—These are *killed* organisms of infection, except the virus of vaccinia, administered hypodermically to cause active immunity.

A. *VACCINA BACTERIALIA*, 7.—A sterile suspension of micro-organisms or a sterile extract or derivative of micro-organisms.

These are (a) *Vaccinum Acnes* (in 1 ml. 20, 100 or 1000 million of specific bacilli). DOSE, Therapeutic 5 to 1000 million at 3 to 10 days' interval.

(b) *Vaccinum Choleraicum* (in 1 ml. 8000 million of *V. cholerae*). DOSE, prophylactic 0.5 ml. : after 7 to 14 days 1 ml.

(c) *Vaccinum Dysentericum Flexner* (in 1 ml. 100 million of each of V, W, X, Y and Z types of the bacilli). DOSE, prophylactic 0.5 ml. : after 7 to 14 days, 1 ml. once or twice.

(d) *Vaccinum Pertussis* (in 1 ml. 1000 to 10,000 million organisms). DOSE, prophylactic, 1000 to 20,000 million on 4 or 5 occasions at 1 to 7 days' interval : therapeutic, 500 to 10,000 million organisms at 1 to 7 days' interval.

(e) *Vaccinum Pestis* (in 1 ml. 2000 million organisms). DOSE, 0.5 to 1 ml.

(f) *Vaccinum Staphylococcicum* (in 1 ml. 100 to 1000 million). DOSE, therapeutic 10 to 1000 million at intervals of from 3 to 7 days.

(g) *Vaccinum Tuberculinum* (in 1 ml. 0.00001 mg. to 0.1 mg.). DOSE, therapeutic 0.00001 mg. to 0.1 mg. at intervals from 3 to 7 days.

(h) *Vaccinum Typho-paratyphosum*, T.A.B. Vaccine (in 1 ml. 1000 million of typhoid, 500 million each of paratyphoid A and B). DOSE, prophylactic : 0.25 to 0.5 ml. : after 7 to 21 days 0.5 to 1 ml.

B. OTHER VACCINES, 3 are prepared from *rickettsiae* or from *viruses*.

(a) *Vaccinum Vaccinae* (Material obtained from vesicles produced by inoculation of vaccinia virus on the skin of healthy animals). DOSE, 1 min. or 0.06 ml. by scarification.

(b) *Vaccinum Typhi Exanthematici* (Sterile killed suspension of rickettsiæ). DOSE, 4 to 15 min. or 0.25 to 1 ml. subcutaneously.

(c) *Vaccinum Febris Flavæ* (Serum-free, aqueous suspension of chick embryo tissue infected with yellow fever virus 17 D strain). DOSE, not less than 500 LD₅₀ doses subcutaneously.

Alternative Preparations Sanctioned for use in Tropical, Sub-tropical and other Parts of the British Empire

Auranti Cortex.—If bitter oranges are not available, dried bitter orange peel or fresh sweet orange peel may be used in preparing tincture of orange.

Extracta Liquida.—If any of these contains ethyl alcohol less than 30% v/v., it may ferment and so this should be increased up to 30%.

Limonis Cortex Siccatus.—If fresh lemon peel is not available, dried peel may be used in preparing syrup of lemon and tincture of lemon.

Unguenta.—If for the temperature, the basis becomes too soft, necessary proportions of benzoinated lard, lard, suet and yellow or white beeswax may be added but the official proportion of the active principles must remain unchanged.

NON-OFFICIAL PREPARATIONS FREQUENTLY IN USE

(1) *Balnea* or baths, usually of 30 gallons, are frequently given of (a) water, cold, of atmospheric temperature (about 80°F) or tepid : (b) water containing antiseptics, weak alkalies, minerals or (c) of hot air. It may be of the whole body, up to the hip (sitz bath) or of a more limited part of the body.

(2) *Buginaria* or *Bougies* are solid elongated bodies containing various drugs and made with gelatin or oil of theobroma for introduction into ear, nose or urethra.

(3) *Cachets* are two watch-glass-shaped halves made of wafer sheet (paste of rice flour and water) into which insoluble or powdered drugs of bad taste are placed and swallowed as a whole with a draught of water. Quinine in powder may be given in this way.

(4) *Capsules* are made of gelatin and these dissolve in the small intestine. Therefore any medicine put inside has no action on the stomach. Carbon tetrachloride, chloromycetin and halibut-liver oil may be administered in this way.

(5) *Collunaria*, *Collyria*.—The former are used as nasal douche and the latter are eye wash. *Collutoria* are paints for mouth and throat.

(6) *Confectio* is a medicated sweetmeat, conserve or electuary, containing honey, sugar or and glycerin in semisolid form, as *confectio senna*.

(7) *Conspersus* is a dusting powder, a mixture of two or more substances, for external use as talc-boric acid powder.

(8) *Emplastrum* is designed to keep a medicinal substance in close contact with the skin by sticking to it, to act as protective

or to approximate the edges of a wound. Various adhesive plasters are prepared.

(9) *Enemata* (Clysters) are liquid preparations given per rectum either for emptying the bowels or to be retained and absorbed: usually made with salines and sometimes an oil emulsified with soap is also used.

(10) *Essentiæ* are solutions of volatile oil in rectified spirit, usually 1 in 5, to be used as flavouring.

(11) *Gargarisma* is a liquid preparation, a solution of one or more substances in water, for gargling.

(12) *Guttæ* are liquid solutions to be dropped into the eye or ear, as *guttæ atropinæ sulphatis*: *guttæ phenolis*.

(13) *Haustus* is a single dose of a liquid preparation to be taken at once as *haustus chloral-bromide*.

(14) *Insufflations* are powders meant to be blown into a cavity such as throat as far as the larynx.

(15) *Irrigatio* is a solution for use as vaginal or urethral douche as *irrigatio zinci permanganatis*.

(16) *Linctus* has syrup, honey or a similar sweet and sticky substance meant to be licked or swallowed slowly as *linctus codeinæ*.

(17) *Magmas* or milks are watery suspensions of white bulky preparations as milk of magnesia.

(18) *Naristillæ* are nasal drops, aqueous or oily, for instillation into the nostrils with a pipette as *menthol-chlorbutol-liquid paraffin drops*.

(19) *Nebulæ* are solutions aqueous, alcoholic, glycerinated or oily used as spray for the air-passages.

(20) *Pastillus* is lozenge prepared with glyco-gelatin basis.

(21) *Pessus* or Pessaries are solid preparations meant to be introduced into the vagina.

(22) *Pigmentum* is a paint for many external surfaces, skin or mucous membranes for its antiseptic, astringent, analgesic or caustic properties: *menthol-aconite paint*.

(23) *Solvellæ* are solution-tablets usually intended for external use by dissolving in water as *mercury-iodide tablets* used for making antiseptic lotions.

(24) *Vapores*.—Volatile drugs are given by inhalations as *benzoin-eucalyptus* in alcoholic solution for use in boiling water.

(25) *Vina*.—Weak tinctures, the active substances of the drug being extracted with sherry as *vinum ipecacuanha*.

(26) *Vitrallæ* are crushable glass capsules protected by a fabric wrapping intended for inhalation of a medicament after crushing as of *amyl nitrite*.

PRESCRIPTIONS

WRITING A PRESCRIPTION.—Great care and skill are necessary in writing a prescription. A large part of the success of a general practitioner depends upon his being able to make an agreeable, decent-looking and effective combination. *Sweetening*

agents as syrups, glucose, glycerin, saccharin and chloroform and *flavourings* as various volatile oils should be added to disguise the unfavourable taste and smell of the active items in the prescriptions.

A good theoretical knowledge of drug action is, however, to be combined with these niceties.

Prescriptions for children should preferably be a palatable *mixture* containing a large proportion of syrup : often be *elixirs* and occasionally, *pastilles*, *drops* or *powders* to be taken with honey or milk. They take castor oil comparatively well. Susceptibilities of children to certain drugs (p. 14, 21) should be kept in mind.

Every item of the prescription should be written in a clear and well-defined language and every bit of it must be easily readable. More active ingredients should be written first. All ambiguous abbreviations should be avoided. No prescriber should depend on the efficiency of the dispenser to uphold his professional reputation by covering up his deficiencies.

After writing out the prescription, read it carefully and if any dose is prescribed in excess of the pharmacopœial limit with a definite purpose, initial it. Lastly, when the checking is complete, initial the prescription. In the prescription for a child, it is good rule to put down the age of the child also just below the name and in that way errors in dosage are best avoided.

Further, the pharmacopœia (1948) directs, *solids* should be prescribed in grains (gr.) and in ounces (oz. = 437.5 grains) and *liquids* in minims (min. or m.) and in fluid ounces (fl. oz.) ; and the quantities should be written in Arabic numerals.

The symbol G. should be used for gramme to differentiate it from gr. (grain).

THE COMBINATION.—Several drugs are often combined in a prescription. These may be divided as follows :—

- (i) **THE BASIS.**—The main drug whose action is most desired.
- (ii) **THE ADJUVANS.**—Auxiliaries, meant to assist the action.
- (iii) **THE CORRIGENS.**—Drugs added to correct the bad taste or any disagreeable action of the principal drugs.
- (iv) **THE VEHICLE** or constituents.—The final make-up or the excipient.

THE FORM OF A PRESCRIPTION : it should run thus,—

Patient's name.—For X. Y. Z.

Superscription.—R (Recipe, take thou)

Inscription.—Hydrargyri Subchloridum gr. 2 (*basis*)

Podophylli Resina gr. $\frac{1}{2}$ (*adjuvant*)

Extractum Belladonnæ siccum gr. $\frac{1}{4}$ (*corrigent*)

Glycer. Trag. q.s. (*constituent*).

Subscription.—Fiat Pilula. Mitte 6

Signature.—One to be taken at bed-time.

Doctor's initial and date.

A. B. C.

The dispensing room should be well lighted and separate from the sale room and no one should be allowed to enter except the dispensers. The tables, racks and shelves should be clean and well placed.

Details of the Prescription :

It will appear that a prescription has 5 parts. These are *superscription* which indicates, "Take thou". Then comes *inscription* or the different drugs prescribed. The third part is *subscription* or the instruction to the dispenser as to what he is to prepare. The fourth part is *signature* or *direction* to the patient and the fifth is *doctor's initial* and *date* at the left hand side or at the bottom.

Others split it up into 7 parts, by adding patient's name and date as separate items.

DISPENSING A PRESCRIPTION

The dispenser should be clean and very careful as any inattention, even apparently slight, may be fatal to the patient and a dirty dispenser creates a very unhappy impression on the patient.

He should have the following requisites :

(i) An accurate *balance on a stand*, which should have at least one removable glass pan. It should be clean, measure accurately and be tested frequently. The weights should also be clean and not too worn out or old. The weight

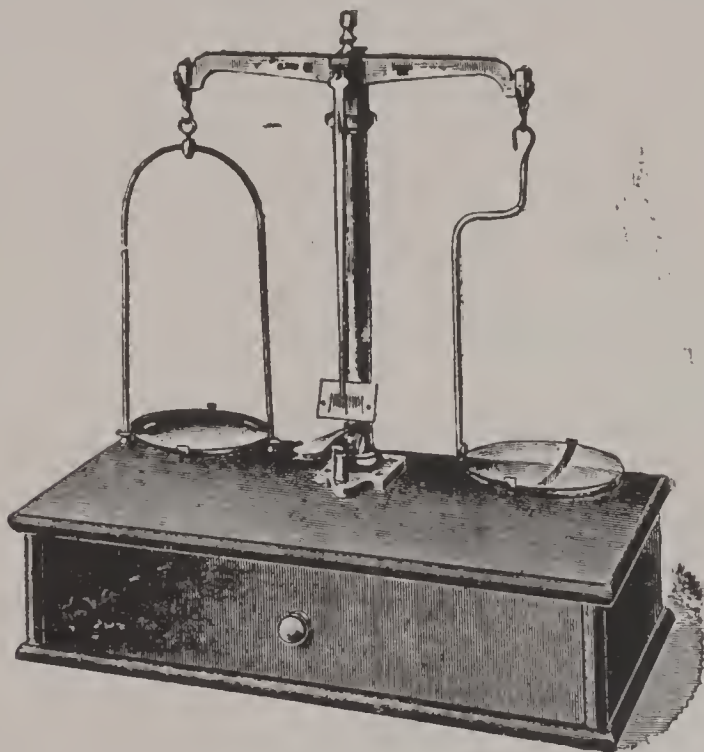


Fig. 1.—Dispensing Balance

should be put on the brass pan and the drug on the glass pan. Except for measuring corrosive substances, which is done on the glass pan only, two bits of paper of exactly the same size should be used, one on each pan. A delicate chemical balance is also necessary for measuring minute quantities of poisonous drugs.

(ii) For measuring liquids, 3 sets of *measure glass* are usually necessary,—a minim glass, an one-ounce and a six ounce measure glass. A conical

measure glass is preferable being easier to clean, more stable and the liquid measured with it forms a wider meniscus.

(iii) Two clean *slabs* either of porcelain or of marble, one for making pills and the other for ointments :

(iv) Four iron *spatulæ*,—two flexible and two stiff : if possible, two bone or box-wood *spatulæ* should also be kept.

(v) A pair of each of Wedgwood ware and glass *pestles* and *mortars* : the former is suitable for general use. It is used in the following way : For grinding and levigation, a flat-headed pestle is taken, grasped with the right hand and is slowly rotated inside the mortar in anticlockwise direction. For mixing and trituration, it is held like a pen and swiftly rotated. For making a pill mass, the end of the pestle is held in the palm of the right hand and the mortar in the left hand, the former being pressed against the latter.

(vi) Emplastrum (spreading) *spatulæ*, infusion and decoction pots, pill cutting and coating machines, suppository mould, cachet filling machine, cork screws, a good supply of dispensing bottles of various sizes, new and assorted "velvet" corks and decent label books should be ready. The mixtures are dispensed in white, liniments in blue and lotion containing drugs acted on by light, in amber coloured bottles. Stock bottles for immediate use should be neatly arranged on the dispensing counter. These must have bold and if possible, permanent labels etched on the glass.

GENERAL INSTRUCTIONS TO THE DISPENSER

(i) Read the prescription carefully, scrutinize the dose, incompatibility, if any, and note carefully whether the quantity ordered is meant for the whole preparation to be divided into several doses or for one single dose. Next, fix it on a holder in front to have it in view during the whole period of dispensing.

(ii) Write out the label and allow it to dry. Also copy the prescription in the special book kept for the purpose.

(iii) In preparing a mixture, mix the different ingredients in the order they would mix best. The salts and various other solid drugs should first be mixed with the solvent ordered in the prescription before the whole vehicle is added.

(iv) Every item should be carefully measured and there should be no guess-work. Minims should always be measured and not dropped.

In pouring liquids out of the stock bottles, care should be taken to keep the label up so that if it is of paper, it may not be spoiled by the fluid trickling down. The stopper should be held by the little finger of the left hand and measure glass by the index and the middle fingers perfectly vertical. Into the latter, the drugs should be poured by holding the bottles with the right hand.

(v) In case of an overdose in any item, look for the prescriber's initial and if that is not present, send back the prescription with a note for initialling the overdose.

No verbal communication or remarks should in any case be made to the party. These are not only unnecessary and likely to create misunderstanding, but are also grossly improper and unprofessional.

(vi) In case of any apparent incompatibility try to make out if that could be intentional or avoidable.

If there is a precipitate, make out carefully if any poisonous or undesirable compound is formed thereby : or if this can be avoided by an intelligent manipulation. If not, dispense the prescription and put "shake the bottle" label. The precipitate should in no case be filtered off.

(vii) Great care should be taken in measuring fractions of a grain or of a minim.

The general rule is to convert the quantity required to the lowest vulgar fraction. Then weigh the least weighable quantity (*e.g.* 1 gr.), add sufficient inert substance to make up to denominator, take the numerator of the trituration and reject the rest.

If in a pill, 1/60 gr. of atropine sulphate is prescribed and 8 pills are ordered, the total quantity of atropine sulphate required will be 8/60 or 2/15 gr. Therefore take one grain of the salt and then thoroughly mix it with 14 grains of sugar of milk to make it 15 grains. Of this now take only 2 grains and destroy the remainder at once. The liquid preparation may be dealt with in the same way by diluting it with distilled water or any other bland solvent. It is better to take at least 5 as the unit as less than 5 min. cannot be measured in a measure glass. These powerful preparations should *always be added last of all* to avoid the mistake of putting these twice.

(viii) Some additional precautions are necessary with poisonous drugs.

Storing.—All poisonous drugs should be placed in a separate shelf under a separate lock and key. These should be labelled in red colour, marked '*Poison*' in English as well as in local vernaculars, and stocked in the blue bottles of special shape.

Dispensing.—Special care should be taken in dispensing these drugs. If these are ordered to be taken internally, the dose and incompatibility, if any, should be specially scrutinised. Medicines for external application, if liquid, should be dispensed in special triangular blue bottles. These should be labelled "*Poison*" and marked "*not to be taken : For external application only*". If any mishap would happen for bad labelling, all the responsibility will be on the dispenser.

Special care should be taken in dispensing opium and cocaine preparations. In either case, the prescription should state clearly the name, age and address of the person prescribed for and the name, address and qualification of the prescriber, also his registration number. All such prescriptions, especially for cocaine and morphine, should be retained and filed to comply with excise rules and the patient should be given only a copy for reference. The quantity of the drug dispensed should be entered in the special stock ledger

(ix) In the case of a mixture, the made up substance is poured into the delivery bottle ; the label and a neatly prepared paper graduation mark are pasted. Bottles with accurately moulded graduations which are usual in a 6 or 8 ounce bottle may be used if available. If froths are formed in the bottle, a few drops of alcohol will dispel them. The cork and if possible a paper capsules also are applied on the top and a paper wrapper is often given.

(x) Before delivery, the prescription is read again to be satisfied that everything has been done correctly.

(xi) No prescription containing habit-forming or cumulative poisonous drugs should be repeated without the knowledge and sanction of the prescriber.

DIRECTION FOR THE PATIENT.—These should be clearly written. How frequently and with what relation to food the medicine is to be taken should be stated. The following rules are usually followed.

(a) Digestants as pepsin, papain, pancreatin and hydrochloric acid also irritants as arsenic, iron, quinine and mepacrine

are to be taken after food : the same may be said of vitamin products and of calcium. (b) Stomachics and bitters are taken half hour before food. (c) Systemic alkalisers are better given between meals. (d) Slowly acting purgatives as anthracene pills are given at bed time but rapidly acting ones as castor oil or salines in the early morning. (e) Hypnotics and sedatives are better given when the patient retires in bed at night.

MAKING UP OF THE DIFFERENT PREPARATIONS

Cachets.—These consist of two halves and made of rice flour and water and are powder receptacles, the object being to avoid bad taste and smell of the powder while swallowing. One whole cachet is placed on the tongue and swallowed entire with a drink of water. The cachets are dispensed by hand and when in large number, with machines.

(i) *Morstad's Type Machine.*—This has three perforated plates which can be opened or superposed, with congruent holes. The halves of the cachets are inserted into the holes in the plate A fitting loosely : on this is swung over plate B which fixes the cachets while filling.

The powder is now introduced with the funnel D and well-pressed in with the thimble E. The lower halves of the cachets being thus filled, the plate B is lifted up. The top halves are inserted into the holes of the plate C which are a little smaller than of B and cachets fit tightly. The edges of the top halves are moistened with the roller F which carries thin mucilage. The plate C is now placed on plate A, the two halves of the cachets being thus exactly placed one on the other. The plate C is next raised and this has all the prepared cachets which are finally pushed out and boxed (*Wet seal cachets*).

(ii) *Cacheteur Secca.*—This is now getting more popular being more convenient to handle. Both halves of the cachets have small knobs which fit into the holes of the two plates up and down. The knobs being of the same size in all cachets, only one machine is sufficient for the whole range. Further no moistening of the edges are necessary, the upper half fitting into the lower like a lid on a box (*Dry seal cachets*). (See figures 2/6 and 2/7).

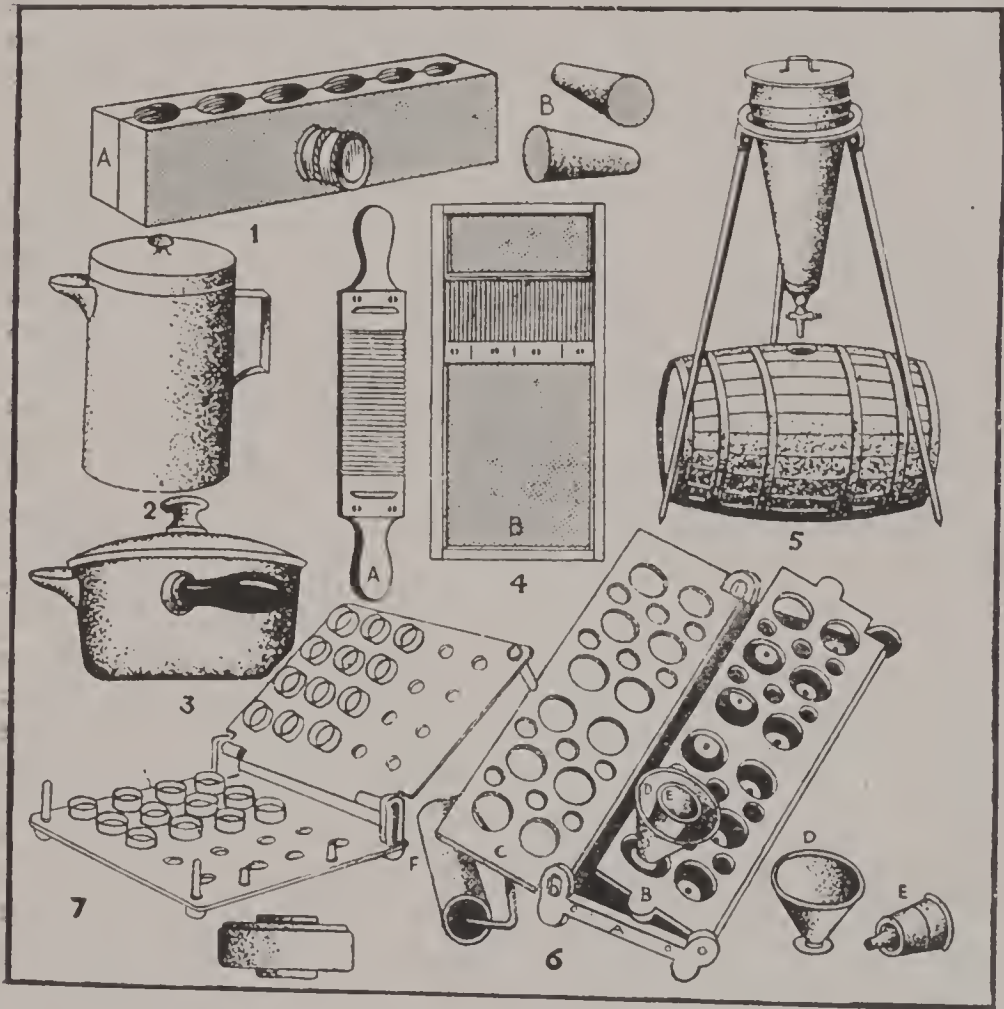
Capsules.—These are hollow, round or ovoid gelatin receptacles (soft capsules) or made of gelatin, acacia and water (hard capsules). These are used for avoiding the taste and smell of the drug and swallowed entire.

SOFT CAPSULES.—These are used for liquids. The stem of the capsule is cut off with scissors. Through the opening so formed, the capsule is filled with the liquid with a hypodermic glass syringe. The cut off stem is melted in water or sand bath and with a heated glass rod, applied to the open end. Finally the whole capsule is dipped into the melted mass and the seal strengthened.

HARD CAPSULES.—These have two cylindrical halves, one slightly larger in diameter and shorter in length. This is the lower half and is put into the hole of a suppository mould or of a capsule filling machine. The required quantity of the powder is poured into this half of the capsule with a small glass funnel, a thin wooden plunger helping the filling. The outer edges are painted with mucilage of acacia and on this, the upper half is fitted. If a soft extract or a liquid is ordered in hard capsules, it is made into a soft mass with a pill excipient and used as above.

If the capsule is meant for intestinal action only, a keratin coating is given (enteric capsules) or the sealed gelatin capsule is soaked in formaldehyde solution for 10 minutes and dried.

PHARMACEUTICAL APPLIANCES



(Bentley)

Fig. 2.—(1) A. Suppository mould. B. A prepared suppository. (2) The infusion pot. (3) The decoction pot. (4) The pillcutting machine: A, the cutter on one side and flat board on the other. B, the flat board and cutting divisions. (First the paste is made: this is rolled on the flat board of B with the same of A to required length: put on the cutting portion of B and divided by the same of A. The cylindrical pieces so obtained are rolled with flat boards of A and B). (5) Percolator. (6) Moist cachet machine (Morstadt type). (7) Dry cachet machine.

Emulsion.—When two immiscible liquids as an oil or resin and water are put together, there exists a separating surface.

By vigorous shaking, this may break and one liquid broken up into globules, becomes temporarily distributed throughout the other liquid. If however a third substance is added, this may concentrate as a film round the dispersed globules and these remain separated for an indefinite period. This third substance is called the emulsifying agent or *emulgent* and the preparation so formed is an *emulsion* which has a milky appearance. (L. *Emulgere*, to milk out).

Emulsions with more water than oil (*oil-in-water type*) are meant for internal administration but those with more oil (*water-in-oil type*) are applied externally. For the first, gums especially acacia are the best : casein, saponins, yolk of egg and potash or soda soap are sometimes used. For the second, wool fat, wool alcohol, resins, beeswax and synthetic wax-substitutes and calcium soap are used.

The mucilage of *acacia* should be prepared fresh. More often powdered gum is used. The latter, free from grittiness, is put into the mortar and the oil is slowly added and rapidly triturated till the whole thing is made pasty. Water and flavourings are now slowly added briskly stirring all the time with the pestle. It should make a homogeneous milky fluid and show no free oil globules. A fixed oil requires a quarter of its weight of finely powdered gum : a volatile oil, the half or a little more and an oleoresin, an equal quantity of it.

Gum tragacanth powder does not make as fine an emulsion with a fixed oil. This gum is sometimes used for volatile oils, 10 grains being used in one ounce of the mixture. Tragacanth 1 and acacia 15 is preferred instead of pure acacia. This makes the emulsion thicker and less likely to cream.

All fixed oils have some free fatty acids and the resins have some free resin acid : these have affinity for alkalis. So their emulsification is often helped by adding an *alkali* such as a little of Liq. potassæ or lime water. *Yolk of an egg* has twice the emulsifying power of acacia. Acid preparations make better emulsion with it, acacia cracking. *Casein* dissolved by adding a little sod. bicarb. will emulsify about 10 times its weight of oil : such emulsion should be made with chloroform water as otherwise it may get rancid. Almond oil is emulsified better by adding a little Liq. potassæ. Cod-liver oil requires a little yolk of an egg and lime water for quicker emulsification : for manufacturing a large quantity of the emulsion, mucilage of *Irish moss* is prepared.

Soaps are used for emulsifying medicines for external use as of a liniment containing turpentine oil : gums form a sticky layer on the skin. For fixed and volatile oils 1/10th and for fat 1/5th as much soft soap is required.

A fine-grained stable emulsion of fixed oils may be prepared. Triethanolamine in warm watery solution in quantity equal to 2 to 4% of the oil to be emulsified is added to a mixture of 2 to 5 times as much of stearic or oleic acid and the oil, with constant stirring. The soap so formed makes good oil-in-water emulsion.

Agar is used extensively (usually with gum acacia) for emulsifying liquid paraffin. *Agar* is dissolved in boiling water and incorporated with paraffin previously heated to 50°C.

Agar makes a solution in hot water and when cooled even 0.5% solution sets to a jelly : so it makes thick emulsion : this thickness is minimised by adding a little acacia. Liquid paraffin emulsion may be made with acacia and tragacanth (p. 38) or with acacia and agar : latter is more popular.

For extract of male fern, add its own weight of acacia and triturate well : then slowly add water with constant trituration. It may also be emulsified with fresh milk by constant trituration.

Menthol and Thymol are dissolved in olive oil and emulsified with dry gum as for volatile oils. Camphor is dissolved in 3 times its weight of alcohol and emulsified with diluted mucilage of acacia.

For *waxes*, hot water should be used. *Emulsifying wax*, *monostearin* self-emulsifying and *Lanette wax SX* make water in oil emulsions of a wide range of consistency from ointment-like cream to a fluid preparation, these being able to take up a varying quantity of water.

Saponins as tinctures of Senega and Quillaia on account of their saponin contents will emulsify oils, 30 m. may do for $\frac{1}{2}$ ounce of a fixed oil or 30 m. of a volatile oil. These are suitable for emulsifying alcoholic and acid preparations and do not turn rancid. But the emulsion is not satisfactory and if kept for sometime, it may cream at the top : a few grains of tragacanth will prevent this.

Lozenges.—The ingredients along with fine sugar, acacia powder and flavouring agents are carefully mixed by kneading. The paste so formed is spread on a slab upto required thickness, the margins trimmed and then cut into adequate sizes with a punch : finally dried in a drying chamber.

Mixtures.—These constitute the largest group of prescriptions for internal administration. The advantages : (i) the different remedial agents being in disintegrated form are readily absorbed and produce action : (ii) liquid drugs are more conveniently administered in a mixture and (iii) certain substances for their physical properties can best be given in dilute solution in mixtures as most of the salines. While a single dose is called "*haustus*" or a draught, several doses in one bottle is "*mistura*" or a mixture.

Considerable skill is necessary in preparing an elegant mixture. It is not binding on the dispenser that he should mix the different ingredients in the same order as they have been prescribed. He must scrutinize the presence of any incompatibility and how best he can avoid chemical decomposition and ensure solubility and with these objects in view, he must know how best to make his way through.

It is a good rule to mix together all the *alcoholic preparations* first. To this alkaloids, volatile oils and resinous constituents should be added and if necessary, a little mucilage also. *Salts* are to be separately dissolved: some are easily soluble simply by stirring as ammon. chlor. or calc. chlor. but others require powdering as ammon. bicarb. or calc. lact. before the vehicle is added: others again dissolve best in warm water but some of these may separate out when cooled and 10 grains of compound tragacanth powder per ounce may be necessary for diffusion. A *vegetable extract* is made into a paste in a part of the vehicle and to this all the flavourings and alcoholic preparations should be added. Last of all, the rest of the vehicle is to be added to finally make it up. Powerful and poisonous drugs should be separately mixed and added last of all. Distilled water makes a better mixture than tap water. The scale preparations are likely to form a sticky mass: these should be carefully dissolved in the vehicle. If the ingredients are likely to have chemical action if mixed in a concentrated form, these should be diluted well before mixing.

If the prescription has any volatile substance as spirit of nitrous ether or ethereal tincture of lobelia, these should not be added to a warm vehicle.

Essential oils, creosote, camphor and resinous preparations are first dissolved in alcohol and water is slowly added: compound tragacanth powder 10 grains per ounce of the mixture is next added and the whole thing is triturated well. Quinine is first dissolved in a diluted acid and the vehicle is next added: if prescribed with an alcoholic preparation quinine is dissolved in it and a little mucilage of acacia should be added to the vehicle to prevent separation.

An insoluble substance but diffusible as light kaolin or light magnesium oxide is first triturated in the mortar with about $\frac{3}{4}$ th of the vehicle and the rest gradually added: a fairly uniform diffusion is obtained. But one like a bismuth salt is better mixed with compound tragacanth powder first, not acacia which forms hard lumps: a little of the vehicle is added and the whole rubbed in the mortar into a smooth homogeneous cream. Phenacetin is similarly used. Then more vehicle is added to complete suspension. In such cases "shake the bottle" label should be applied.

Ointment.—The ointments may be classified as follows.

(i) *Ointments prepared by fusion.* The ointment base may be a single fatty substance as soft paraffin but more often it is an admixture by melting of several substances as ointments of paraffin, emulsifying wax, wool fat and wool alcohols of B.P.

(ii) *Ointment emulsions* as made with wool fat, wool alcohols, soap (fatty acid and triethanolamine combination now preferred) and esterified wax such as Lanette wax SX bases are now more extensively used these being capable of absorbing a fair amount of water (making oil-in-water or water-in-oil emulsions) and the resulting preparation is a more agreeable cream-like substance.

(iii) *Ointments are prepared by trituration* of an insoluble medicament first finely powdered, with a suitable fatty base: most of the usually prescribed ointments belong to this group (salts of mercury, boric acid, dithranol, sulphur and zinc oxide ointments are the common examples): sometimes as with iodine and metallic salts, an oleic acid combination helps better mixing. In order to ensure a thorough mixing of the drug and the basis, a small quantity of the former should be mixed with a part of the basis and gradually more and more of either should be added. Trituration must be continued till a homogeneous smooth paste is obtained.

A hard and gritty substance as sulphur or a mercurial, should be well triturated on the slab with the spatula and if the quantity is large, pestle and mortar should be used till all grittiness disappears. Resinous or balsamic substances should be first rubbed down with a softening agent as alcohol (90%), glycerin, oil or water. Alkaloids should first be dissolved in oleic acid with gentle heat: this ensures uniform mixing with the basis.

Perchloride of mercury is preferably made into a paste with double the amount of glycerin, and chrysarobin with castor oil, before the basis is added. Phenol ointment should be made with liquid phenol. A liquid vegetable extract should be thickened by evaporation. A volatile substance should be mixed last of all.

CHOICE OF THE BASE.—The different bases as (i) *hydrocarbons* (soft paraffin, hard paraffin ointment), (ii) *lard* (animal fat), (iii) *wool fat* and *wool alcohol* and (iv) *synthetic wax-like substances* (emulsifying wax) are used. (a) Paraffins do not readily penetrate the skin and in most of the B.P. preparations meant for local action only on the skin, simple ointment (combination of hard paraffin, soft paraffin and wool fat) is used. (b) Lard or benzoinated lard is now seldom used as it may turn rancid: these can however moderately penetrate the skin. (c) Wool fat penetrates well especially if mixed with water which it can take up about 50% and mixed with soft paraffin it forms eye ointments basis: the advantages are (i) perfect emulsification of the aqueous solution of the alkaloidal salt (the main medicament) favouring its absorption: (ii) it is of fairly good consistence (soft paraffin alone is too soft) and (iii) is an emollient. (d) Synthetic bases are water-miscible and emulsifying wax is used for making penicillin and other creams. (e) Soap emulsion: fatty acid from animal or vegetable fats or oils with triethanolamine form oil-in-water type of emulsion and is suitable for making "cold cream": the water evaporates causing a cooling action: fat left on the skin is emollient.

Hydrophilic or emulsified ointments are now getting more popular. These (a) do not interfere with the normal function of the skin and are readily penetrating: (b) are more effective bacteriostatic and bactericidal: (c) stable with most of the ointment medicaments and (d) more acceptable cosmetically. The basis may be (i) Lanette wax SX containing a mixture of cetyl, stearyl, and homologous fatty alcohols with about 10% sodium salts of sulphated alcohols or (ii) a mixture of sod. lauryl sulphate 0.5, cetyl alcohol 8, cacao butter 6.5, white petroleum 20 and distilled water 65 (*Gibson's basis*).

Steel spatula should not be used for tannic acid, salicylic acid, iodine, also for chloride, acid nitrate or red oxide of mercury ointments and for oxidising agents. A bone or vulcanite spatula is suitable for the most.

The ointment should be dispensed in a porcelain pot with a wax paper covering. It is even more preferable to use collapsible tubes: these are made of tin. The eye ointments (oculenta) should be prepared with the basis sterilised at 150°C for one hour and dispensed in collapsible tubes.

Pastes.—The pastes are medicated preparations for application on the skin and have either non-greasy bases as gelatin,

glycerin, starch, tragacanth or soap or are made with paraffin. Recently a cellulose ether base (P.M.B. 333) and colloidal aluminium hydroxide (marketed as *Unemul*) are also used as bases.

(a) A 2% hot gelatin solution with 20 to 40% glycerin (preservative) makes a paste with 10 to 15% zinc oxide in fine powder (*Unna's paste*).

(b) To glycerin heated to 140°C in a dish, add starch mixed with water and stir briskly : this makes a translucent jelly into which is incorporated the medicament as resorcin or ichthyol.

(c) A paste is made with tragacanth and glycerin each 5 and water (by weight) 95 by trituration (*Bassorin paste*): into this the medicament is added.

(d) Bismuth subnitrate 1, Iodoform 2 and Liquid paraffin 1 or q.s. are triturated in a sterile mortar to make a smooth paste (*B.I.P.P.*). *Pasta Zinci Composita B.P.* also belongs to this group.

Pills.—The *advantages* of pills are : (i) these are convenient method of administering drugs with unpleasant taste : (ii) these keep well fairly long and (iii) these are easily portable. These to be of value *should* (a) disintergrate easily in the intestine, (b) should be of uniform size and neat looking and (c) should be tasteless : for this sugar-coating or varnishing may be necessary. (d) A pill *should not be* too bulky nor too small : (e) it should not be too hard nor too soft nor sticking together and (f) should be quite spherical. It should not be more than 5 grains and if the ingredients are less than one grain, the quantity should be increased to at least one grain or a little more. by adding usually powdered liquorice in case of coloured pills or sugar of milk in case of white pills.

(1) The solid ingredients are first finely powdered by careful trituration in a mortar and the excipient is then added in small portions and thoroughly kneaded with the powder, the pestle being held rigidly forming a straight line with the wrist and forearm, till a homogeneous mass of proper consistency is obtained. This mass is removed from the mortar completely no scraps being left behind.

(2) A few grains of talc are sprinkled on the flat board of the pill machine and the mass is rolled into a uniform cylinder of required size (depending on the number of pills to be made), ends not tapering, and cut by the pill-cutter. The cylindrical pieces obtained are next rolled on a slab to make them round.

(3) The quantity of the excipient should be carefully adjusted. If the pills are too soft and so liable to lose shape, some fibrous materials as lycopodium or liquorice powder should be added. The pills are dispensed out in small circular boxes and their sticking together in the box may be prevented by putting French chalk, carbonate of magnesium, cinnamon, lycopodium or liquorice powder in the container.

A powerful and poisonous ingredient should first be well mixed with some dry powder and then the other ingredients are slowly added and triturated. But if added straight way to the pasty excipient, it would be difficult to mix it uniformly

and some pills may have it in greater proportion than others. So these should be slowly added in the diluted form, bit by bit to the excipients, triturating again and again. A volatile oil in a pill is similarly treated. This mixing should be done with a Wedgwood ware pestle and mortar or if the quantity is small, on a porcelain or marble tile with a spatula.

EXCIPIENTS.—These are either a thick, sticky fluid, powdered gum, absorbent or mucilage containing vegetable powders or certain inert chemical substances meant to make a cohesive pill mass. Incompatible or bulky excipients are not used.

ADHESIVE EXCIPIENTS.—*Acacia powder* may be used for making pill mass of gritty substances in combination with syrup of glucose but the pills are liable to be rather hard.

Glucanth consists of tragacanth 1, glycerin 3, water and syrup of glucose 6. This is a good and cohesive excipient.

Liquid glucose is good for Ferrous carbonate pills. Sometimes syrup of glucose is also used with acacia and is a good excipient for many.

Glycerin of tragacanth is an excellent excipient but should be used sparingly otherwise the pill mass will be too elastic to be spherical.

Tincture of Gentian and *treacle* and also *Extract of Gentian* or of *Taraxicum* are sometimes used for many pills: but these are not very adhesive.

SOLVENTS OR SOFTENING EXCIPIENTS.—*Alcohol* (90%) is used for dissolving substances like camphor or resinous extracts which are then quickly massed with powdered liquorice root and a little powdered tragacanth or syrup of liquid glucose. Dilute alcohol may be similarly used for scale preparations of iron.

Distilled water is useful in making a pill mass of Quinine acid hydrochloride and also for substances containing aloes, gum and water-soluble vegetable extracts.

Glycerin is very hygroscopic and therefore the pill becomes soft. But it is useful for iron and tannic acid pills which are liable to become hard.

Castor oil with powdered soap is an excipient for camphor pills.

ABSORBENT EXCIPIENTS.—*Calcium phosphate* is used to give bulk and absorb fatty substances and essential oils.

Kaolin is an adsorbent powder which with vaseline forms good excipient for oxidising substances like potassium permanganate and silver nitrate.

Lanolin may be used to make pills of scale preparations.

Liquorice powder is a good absorbent and the fibres have mechanical stiffening effect and therefore makes excellent pill mass with a suitable cohesive substance and is helpful for hygroscopic and soluble salts.

Milk sugar is non-hygroscopic and is a suitable vehicle for diluting alkaloidal salts and similar powerful substances. The pill mass is made with a suitable cohesive substance as glycerin of tragacanth or syrup of glucose.

Soap.—Powdered hard soap or curd soap is used for volatile oils which renders them more miscible with other ingredients and less liable to separation from the mass. This is also very suitable for massing creosote, powdered camphor or resin, and is combined with syrup of glucose or powdered liquorice.

Wax or anhydrous wool fat is melted and added to hygroscopic, oily or very soluble substances.

EXCIPIENTS FOR SPECIAL DRUGS MADE INTO PILLS

Freshly made pills have been largely replaced by tablets and machine-made commercially prepared pills. Some pills are however yet freshly made: these are meant for immediate use.

ALKALOIDAL PREPARATIONS.—The required quantity is measured (p. 69) and massed with sugar of milk or liquorice powder and then made up with glycerin of tragacanth.

ALOES.—With hard soap and syrup of liquid glucose.

ALOIN.—With glycerin of tragacanth or hard soap.

BUTYL CHLORAL HYDRATE.—Prepared with glycerin of tragacanth.

CAMPHOR also menthol, betanaphthol or thymol.—First powdered by dissolving in alcohol and evaporating; it is then made up with hard soap and syrup of liquid glucose.

CHLORBUTOL is made up with acacia and syrup of glucose.

CINCHOPHEN is made with soap and glycerin of tragacanth.

CREOSOTE, PHENOL.—First massed with liquorice powder and soap and made up with a cohesive excipient like glucanth.

EMETINE BISMUTH IODIDE may be made up with tragacanth and acacia mucilage afterwards coated with keratin or salol.

FERROUS SULPHATE.—First pulverised, massed with sugar of milk and then made up with syr. of liquid glucose or glycerin of tragacanth. *Scale Preparations* are massed with lanolin and kaolin: or massed rapidly with 45% alcohol.

HYDRARG. C. CRETA, HYDRARG. PERCHLOR.—First massed with a little sugar of milk and made up with glycerin of tragacanth or syrup of liquid glucose.

PEPSIN.—Five grains of pepsin is made up with one minim of dilute hydrochloric acid.

POTASSIUM IODIDE.—First rubbed with a little water and then a bland vegetable powder like liquorice is added.

POTASSIUM PERMANGANATE is made up with kaolin and hydrous wool fat or vaseline. The same excipient is suitable for other oxidising agents and for silver nitrate. These are however rarely used.

QUININE SULPHATE is made into a paste with a small quantity of citric or tartaric acid or half its volume of cream of tartar. As pills become soft in damp weather, a little powdered acacia may be helpful.

QUININE ACID HYDROCHLORIDE is massed with a minute quantity of water: and an excess makes the pills soft.

SALOL is made with glucanth.

VEGETABLE POWDERS.—Make a mass with acacia and tragacanth in equal parts and syrup of liquid glucose. Dry vegetable extracts are massed with alcohol 45%, one drop for every 4 grains and quickly made into pills. A soft extract is evaporated to pill consistency and made up with powdered acacia.

VOLATILE OILS.—Use $\frac{1}{2}$ gr. of curd soap and $1\frac{1}{2}$ grs. of powdered liquorice for each minim of the oil.

PILL-COATING

The coated pills are tasteless, elegant in appearance and keep better. Sometimes it is desired not to allow the pill to dissolve in the stomach and it is coated with sandarac resin, shellac, keratin, salol, or gelatin which allows

the pill to pass down into the intestine where only the coating is dissolved by the pancreatic juice and the medicine is liberated.

Sandarac coating.—The solution is prepared by dissolving 1 of sandarac in 2 of alcohol (90%) and 10 of ether. A few drops of it are put on the pills in the varnishing pot, gently shaken up and dried. One coat may do but sometimes two are necessary.

Shellac dissolved in cetosteryl alcohol may be used for enteric coating.

Keratin coating.—The pills should be prepared with a fatty excipient dipped in melted cacao-butter and then covered with 2 to 3 coatings of keratin solution. (Keratin 9, strong solution of ammonia 45.5 and alcohol 90%, 45.5).

Salol coating.—The pills are coated with salol varnish consisting of salol 20, shellac 30, solvent ether 30 and dehydrated alcohol upto 100.

Pearl coating.—The pills are placed in a pot containing mucilages of acacia and tragacanth and syrup in equal parts. These are next put into another pot containing fine talc, 30 grs. for 12 pills, and shaken. Talc forms a coating which if thin, more talc may be put in. Finally the pills are polished by rotating in a third empty pot. The pills do not easily disintegrate and this is the disadvantage.

Silver coating.—Silver leaves are available. The pills should have a polished surface, free from powder and fairly firm. A minimum quantity of mucilage of acacia is now applied on the pill surface to make it sticky and then the pills are carefully dropped on the leaf in the silverer which is carefully rotated.

Gelatin and Sugar coatings are given with machinery only and are not within the reach of usual dispensing work.

An improvised gelatin coating may be given by dipping the pills in a solution still hot, made of gelatin 1 and water 4, melted in water bath. The pills formed are sometimes dipped in formaldehyde solution and then dried. (*glutoid coating*). This makes the pills insoluble in the stomach but soluble in the intestine.

Plasters—These are intended to give *support* to any part, to *protect* and approximate a wound surface (adhesive plasters): to *apply some medicines* to the skin, generally an analgesic, for slow absorption or a blistering medicine for counterirritation (medical plasters). Only the *adhesive plasters*, are now frequently used.

All blistering plasters must be freshly made. The other plasters are available in the market, machine spread, made into rolls and the dispenser is only required to serve these according to the size ordered. Some of these are also prepared in the dispensing counter.

The adhesive plaster masses are prepared with (a) natural or synthetic resins or (b) para rubber, pale crepe rubber or smoked sheet rubber of first quality. The medicated plasters have the specific medicine in the adhesive mass.

Method.—The plaster mass in cylindrical rolls is first taken in a gallipot, about 15 grs. of it being required per square inch and is melted on a flame to creamy consistency stirring all the time. The pattern is first made with a thick brown paper by folding it twice and cutting the central portion to the required size.

The plaster is usually spread on white leather or adhesive-plaster cloth. The latter is cut to a size $\frac{1}{2}$ inch bigger on all sides than what is required, with the rough surface up and the pattern moistened with water is put on it. The melted plaster

is now poured into it and with a warm spatula or plaster-iron, this is carefully spread out. If an adhesive margin is to be kept in it, after the main plaster is spread, a pattern $\frac{3}{4}$ " bigger on both sides is applied and in the outer portion, adhesive plaster is spread.

Mammary plaster is made circular and its margins are notched or making a central hole for the nipple, a small V-flap is removed so as to fit over the breast more neatly.

Blistering plaster.—The pattern which is evidently much smaller is first prepared and then it is put on a piece of adhesive plaster or chamois leather. Cantharidin plaster is spread over in the usual way with a warm spatula. No previous melting of the plaster is however, necessary. An oil paper covering is usually given to it when dispensed which should be removed before application.

Mustard plaster.—This is frequently used for counter-irritation. Mustard paper if available is dipped in tepid water for half a minute and applied. Freshly made plaster as well as poultices are more frequently applied.

The plaster is made by making a paste of mustard powder with the required quantity of cold water and spread on a piece of brown paper by a spatula with the help of a pattern as described above.

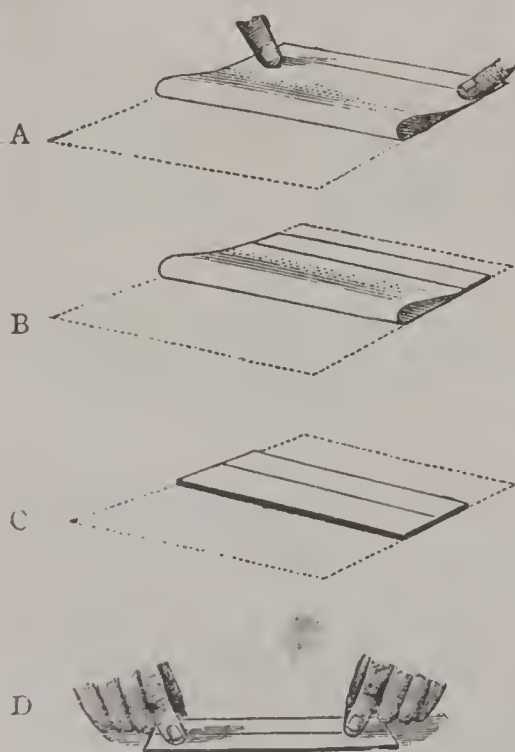
Usually it should be kept on the skin surface for 15 to 20 minutes and then it is removed and on the place a little bland oil applied.

Mustard poultice is made by sprinkling mustard powder on a hot linseed poultice.

Powders.—These may of a single substance and more often of several (compound powders). The different ingredients finely

powdered separately and weighed to the required amount are carefully mixed with a spatula on a slab or with a small pestle and mortar and made into fine, nearly impalpable form.

A powerful constituent should be first triturated with some bland substance and then slowly mixed with the rest of the lot. It should then be packed in white glazed paper. Hygroscopic drugs should be stocked in accurately fitting glass stoppered phials and dispensed wrapped in waxed or paraffin paper and preferably covered with tinfoil also. The dispenser must learn the proper method of folding the paper. Powders for external use should preferably be dispensed in dredgers.



(Bentley)

Fig. 3.—The method of folding the powder packets

Tinctures and soft extracts are partly evaporated and pulverised with lactose. Volatile oils are massed with calcium phosphate or kaolin (10 grains for 5 drops). Those that liquefy when mixed together, are separately

incorporated with the remainder of the ingredients and are finally brought together : those that make pasty mass are dispensed with calcium phosphate.

Suppositories.—These meant for introduction into the rectum, are smooth conical bodies, weighing approximately 15 grains each and rarely bigger, upto 30 grains. Bigger suppositories are sometimes better retained and suitable for adults, especially the torpedo-shaped ones, conical at either end.

The basis for the suppository is mostly *oil of theobroma* and in order to give it the necessary solidity, in the hot months, a certain amount of beeswax may be mixed with it. Cocoanut oil is an inferior substitute for oil of theobroma on account of its softness but may be used, with a larger quantity of beeswax.

DISPLACEMENT VALUES.—The volume of a suppository made from a particular mould being the same, the density of the substance used as compared with the same of oil of theobroma, is important. Alkaloids, alkaloidal salts, solid extracts, alum, borax, phenol, opium and silver proteinate require about $\frac{2}{3}$ to $\frac{1}{2}$ the space of oil of theobroma for the same weight : bismuth subgallate $\frac{1}{3}$ rd, iodoform $\frac{1}{4}$ th, zinc oxide $\frac{1}{5}$ th and lead acetate $\frac{1}{3}$ rd space and tannic acid and all liquids, the same space. So for making a 3 grs. iodoform suppository, $15 - (3 \div 4) = 14\frac{1}{4}$ grs. of basis should be taken to completely fill up the mould. Pessaries and bougies are prepared in the same way in their special moulds.

Method.—The active substance is thoroughly mixed in a porcelain slab with the basis melted in a water bath. This basis should not be hot as then substances like chloral hydrate or iodoform may decompose. An alkaloid dissolved in oleic acid mixes better. If 6 suppositories are to be made, ingredients should be taken sufficient for 8 to make up the unavoidable loss in handling. This is then poured into the mould which should be lubricated with a little soft soap solution or olive oil and previously cooled by placing it either in ice or in cold water. Finally, these should be dispensed out in partitioned boxes or wrapped with wax paper.

Glyco-gelatin base is made by dissolving in water bath gelatin 25, glycerin 40 and water 80 (by weight) evaporated to 100. This may be used for boric acid, chloral hydrate, glycerin, ichthammol and iodine-pot-iod. suppositories. Being heavier, 18 grs. of the base is necessary.

Adrenaline is dissolved in about 10 min. of a 1 in 30 solution of boric acid and added to a mixture of melted oil of theobroma and $\frac{1}{2}$ gr. of sodium stearate for each suppository : stirred till an emulsion is formed and poured into the mould when just setting.

Vegetable extracts.—If dry, treat in the ordinary way : if liquid, concentrate on a water bath : if soft, rub down well on a slab and then add the basis.

Tablets.—These are prepared by putting the material into a hollow cylinder or die and compressing it between two punches.

The substance should be granulated by passing through No. 22 or 30 sieve and dried at a temperature not exceeding 40° . The granules flow through the machine more easily, are uniform in composition and more perfectly knit together into tablets than fine powders. To these are added a *disintegrant* as arrowroot or potato powder or sucrose and an *excipient (binder)* as theobroma emulsion (oil of theobroma 25, hard soap 2.5, powdered,

tragacanth 0·57, benzoic acid 0·45 and distilled water to 100): powdered acacia (5 to 10%) : syrup with an equal part of water or diluted alcohol. The whole thing is thoroughly mixed by pestle and mortar and made into crumbly granules. If theobroma emulsion is used, no lubricant is necessary: otherwise talc (2 to 5%) or liquid paraffin is sprayed on the mass. The punch and die should be of exact size for the weight of the tablets to be made.

COMMONER LATIN PHRASES USED IN PRESCRIPTIONS

| | | |
|-----------------|--------------------------|-------------------------------|
| aa, | ana | of each. |
| A. c. | ante cibos | before food. |
| Ad. | Adde | add. |
| Ad. lib. | Ad libitum | as much as desired. |
| A. h. | Alternis horis | every other hour. |
| Aq. | Aqua | water. |
| Aq. bull. | Aqua bulliens | boiling water. |
| Aq. dest. | Aqua destillata | distilled water. |
| Aq. steril. | Aqua sterilisata | sterilised water. |
| B. d., B. i. d. | Bis die, bis in die | twice a day. |
| C. | Cum | with. |
| Cap. | Capiat | let him take. |
| Cib. | Cibus | food. |
| Coch. amp. | Cochleare amplum | a table-spoonful. |
| Coch. mod. | Cochleare modicum | a dessert-spoonful. |
| Coch. min. | Cochleare minimum | a tea-spoonful. |
| C. m. | Cras mane | to-morrow morning. |
| C. m. s. | Cras mane sumendus | to be taken tomorrow morning. |
| C. n. | Cras nocte | to-morrow night. |
| C. v. | Cras vespere | to-morrow evening. |
| D. | Dosis | a dose. |
| D. d. | de die | daily. |
| d. | da | give. |
| Div. | divide | divide. |
| D. in p. æ. | Divide in partes æquales | divide in equal parts. |
| F. ft. | Fiat | let it be made. |
| F. h. | Fiat haustus | make a draught. |
| F. m. | Fiat mistura | make a mixture. |
| F. pil. | Fiat pilula | make a pill. |
| gr. | Granum | a grain. |
| Gutt. | Gutta, guttæ | drop, drops. |
| H. s. | Hora somni | at bed time. |
| I. c. | Inter cibos | between meals |
| M. b. | Misce bene | mix well. |
| M. d. u. | More dicto utendum | to be used as directed. |
| Mit. | Mitte | send. |
| O. m. | Omni mane | every morning. |
| Omn. hor. | Omni hora | every hour. |
| Omn. bih. | Omni bihora | every 2 hours. |
| O. n. | Omni nocte | every night. |
| Part. æq. | Partes æquales | equal parts. |
| P. c. | Post cibos | after food. |
| Q. s. | Quantum sufficiat | sufficient quantity. |
| R. | Recipe | take. |
| Rep. | Repetatur | let it be repeated. |
| Sig. | Signetur | let it be labelled. |
| S. O. S. | Si opus sit | if necessary. |
| Ss. | Semis | half. |

| | | |
|-----------|------------------|---------------------------|
| Stat. | Statim | immediately. |
| S. S. | Statim sumendum | to be taken immediately. |
| T. d. s. | ter die sumendus | to be taken thrice daily. |
| T. i. d. | ter in die | three times a day. |
| Vac. Ven. | Vacuo ventriculo | on an empty stomach. |
| Vesp. | Vesper | the evening. |

INCOMPATIBILITY

INCOMPATIBILITY has been defined by Smith as "any unintentional change which notably interferes with elegance, usefulness or safety of a prescription." Such changes may be grouped as follows :

1. **CHEMICAL INCOMPATIBILITY** : Here certain chemical interactions take place between the different ingredients.

2. **PHYSICAL OR PHARMACEUTICAL INCOMPATIBILITY** : Here the components do not form a clear solution or it is of an undesirable colour or consistency.

3. **THERAPEUTIC INCOMPATIBILITY** : Here drugs having antagonistic actions are grouped together. This is sometimes done purposely, one being the corrective of the other.

The most dangerous and of greater practical importance is, however, the chemical incompatibility.

CHEMICAL INCOMPATIBILITY

1. Formation of an Insoluble Compound

The salts of calcium, lead, zinc, silver, iron and mercury are most often precipitated by being changed into insoluble oxides, hydroxides, carbonates, chlorides, sulphates, iodides, etc.

(a) **CALCIUM AND MAGNESIUM**.—Of the former, chloride, bromide, gluconate, iodide and lactate and of the latter, chloride and sulphate are soluble.

A calcium salt is thus incompatible with alkaline hydroxides, carbonates, sulphates, phosphates and soluble oxalates.

A magnesium salt is also similarly incompatible except that it is not precipitated by sodium and potassium carbonate and bicarbonate or ammonium carbonate.

(b) **IRON**.—Its insoluble salts are hydroxides, carbonates and phosphates. An iron salt is therefore precipitated if combined with hydroxides, carbonates or phosphates. The scale preparations, however, do not form precipitates with alkalis.

1. Calc. Chlorid.
Sod. Carb. aa. grs. 15
Aq. fl. oz. 1
(Calcium Carbonate ppt.).
2. Mag. Sulph.
Sod. Phosph. aa gr. 60
Aq. fl. oz. 1
(Mag. Phosph. ppt.).

3. Cal. Chlorid. grs. 15
Sod. Sulph. grs. 30
Aq. fl. oz. 1
(Calcium Sulphate ppt.).
4. Ferr. Sulph. gr. 2
Sp. Ammon. Aromat. m. 20
Aq. fl. oz. 1
(Ferr. Carb. ppt.).

Ferric Salts are acid in reaction and should not be used with iodides, bromides, salicylates or benzoates : an alkali salt, if present, may prevent the reaction.

(c) **MERCURY.**—Its oxides and iodides are insoluble and a mercury salt is precipitated by soluble oxides and iodides. "Black wash" (subchloride of mercury precipitated by lime water with the formation of mercurous oxide) and "Yellow wash" (perchloride precipitated in the same way, forming mercuric oxide) are intentional though apparently incompatible preparations.

Potassium iodide with perchloride of mercury throws out red iodide of mercury but this precipitate is again soluble in excess of iodide and therefore a combination of Liq. Hydrarg. Perchlor. and Pot. Iod. makes clear solution and is often prescribed.

Again aromatic spirit of ammonia with mercury perchloride causes precipitation of ammoniated mercury : with 10 grains of compound tragacanth powder per ounce added, the prescription may be served and "shake the bottle" label given.

(d) **LEAD.**—Acetate and subacetate are soluble and the rest are all insoluble. Lead is therefore incompatible with a large group of drugs as oxide, carbonate, sulphate, sulphide, iodide, bromide, phosphate, tartrate, benzoate, citrate, salicylate, tannate, etc. Gum arabic is precipitated by lead subacetate.

(e) **ZINC AND COPPER.**—Their salts are incompatible with alkaline hydroxides, carbonates and phosphates : also with borax, insoluble compounds being formed.

(f) **SILVER.**—The only soluble salt is nitrate and so a silver salt is precipitated by many but the commonest precipitant is a soluble chloride. Therefore no silver lotion should be made with tap water which contains chlorides, distilled water being used instead.

Silver is also incompatible with alkaloidal hydrochlorides as morphine or cocaine hydrochloride : their nitrates are prescribed with silver nitrate.

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|----------------------------------|-----------------------------------|
| 5. Acid. Tann. gr. 20 | Aq. fl. oz. 1 |
| Liq. Plumb. Subacet. | (Zinc. borate ppt.). |
| Dil. fl. oz. 4 | 10. Liq. Ferr. Perchlor. |
| (Lead tannate ppt.) | Acid. Phosph. Dil. aa m. 15 |
| 6. Mag. Sulph. gr. 60 | Aq. fl. oz. 1 |
| Sod. Carb. gr. 15 | (Ferr. Phosph. slowly ppt.). |
| Aq. fl. oz. 1 | 11. Liq. Hydrarg. Perchlor. m. 60 |
| (No ppt.). | Sp. Ammon. Aromat. m. 20 |
| 7. Cuprum. Sulph. gr. 4 | Aq. fl. oz. 1 |
| Tinct. Kramer. m. 60 | (Ammoniated mercury ppt.). |
| Aq. fl. oz. 1 (Cupr. tann. ppt.) | 12. Argent. Nit. gr. 10 |
| 8. Pot. Iod. gr. 5 | Cocain. Hydrochlor. gr. 4 |
| Liq. Hydrarg. Perchlor. m. 20 | Aq. fl. oz. 1 |
| Aq. fl. oz. 1 | (Silver Chlor. ppt.). |
| (Red iodide is dissolved in | 13. Argent. Nit. |
| excess of iodide, no ppt.) | Zinc. Sulph. aa. gr. 4 |
| 9. Borax gr. 15 | Aq. fl. oz. 1 |
| Zinc. Sulph. gr. 2 | (Silver Sulph. ppt.). |

Like other metallic salts, it is incompatible with alkaline hydroxides and carbonates, iodides, phosphates and tannic acid.

Dispensing may be possible in some cases by (i) dissolving the offending substance in the maximum amount of the fluid vehicle before its admixture with other substances or by (ii) using compound tragacanth powder 10 gr. for each ounce of the mixture to the offending substance, provided the precipitate is not objectionable from therapeutic point.

2. Evolution of Gas which may cause Explosion—

(a) A carbonate or bicarbonate combined with a stronger acid liberates CO_2 . This is sometimes done intentionally in order to make effervescent mixtures, the acid and the alkali carbonate or bicarbonate being dispensed separately and combined at the time of administration.

In the same way, chlorate of potash is mixed with hydrochloric acid to evolve chlorine gas.

A combinations of an acid with an alkali should be avoided unless the object is to form a new product.

Some organic preparations are inactivated in alkaline solution: these are, adrenaline, insulin, pepsin and posterior pituitary extract. Pancreatin in the same way is destroyed in acid solution.

Commoner acid and alkaline preparations that one is apt to forget are noted below. Though such combinations would not in all cases evolve gas (CO_2), yet these should, for obvious reason, be avoided.

Acid preparations.—Acids, Acid Salts, Liq. Ferr. Perchlor., Acetum and Oxymella, Ext. Ergot Liq., Ext. Cinchon. Liq., Liq. Adrenalin. Hydrochlor., Liq. Morphin. Hydrochlor., Sp. Ether. Nitros., Syrup. Easton's, Syrups of lemon and squill.

Alkaline preparations.—Hydroxides, carbonates and bicarbonates, Alkali salts, Liq. Bismuth, Ammoniated preparations and Borax.

Acid salts are generally incompatible with iodides, bromides, salicylates and benzoates (liberating iodine, bromine, salicylic or benzoic acid) and glucosides are decomposed by mineral acids.

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| 14. Pot. Iod. gr. 5 Sp. Ether. Nitros. min. 15 Syr. Scill. m. 60 Aq. ad. fl. oz. 1 (Free iodine liberated) | 18. Liq. Ferr. Perchlor. min. 10 Sp. Ammon. Aromat. min. 20 Aq. ad. fl. oz. 1 (Ferr. Hydras ppt.). |
| 15. Acid. Hydrochlor. Dil. min. 15 Ext. Glycyrrh. Liq. m. 80 Aq. fl. oz. 1 (Glycyrrhizin ppt.). | 19. Pot. Brom. gr. 15 Syr. Limon. min. 60 Aq. ad. fl. oz. 1 (Bromine liberated). |
| 16. Acid Hydrochlor. Dil. min. 10 Sod. Benz. gr. 10 Aq. fl. oz. 1 (Benz. acid ppt.). | 20. Bism. Subnitrates. Sod. Bicarb. aa. gr. 15 Aq. fl. oz. 1 (CO_2 evolved). |
| 17. Pot. Chloras gr. 10 Glycerinum min. 15 Aq. fl. oz. 1 (May be dispensed if Pot. Chlorate is first dissolved in water). | 21. Pot. Permang. 5 Alcoh. (90%) 10 Aq. 25 (Explosive). |
| | 22. Acid. Chromic gr. 4 Glycerinum fl. oz. 1 (Explosive). |

Liquid extract of liquorice, if combined with acids, precipitates glycyrrhizin and should never be given in acid mixtures: partial precipitation takes place with calcium chloride and magnesium sulphate.

(b) Oxidising agents in combination with reducing agents explode or catch fire. The following table shows commoner agents which should never be mixed together. (Udale).

| <i>Oxidising agents.</i> | <i>Reducing agents.</i> |
|---|--|
| Chlorates and hypochlorites | Organic substances as alcohol, |
| Chlorine, nitro-hydrochloric acid. | glycerin, ether, tannin, sugars, |
| Bromine and iodine. | vegetable drugs, charcoal, volatile and fixed oils, creosote, |
| Chromic acid, bichromates, chromates. | pyroxylin, etc. |
| Nitrates. | Arsenious acid. |
| Peroxides, permanganates, persulphates. | Phosphorus, hypophosphites. |
| Lead and silver oxides. | Sulphur, sulphides, sulphites, hyposulphites nitrites, oxalates. |
| Sulphuric acid (with organic matter). | Ferrous and mercurous salts. |
| Cupric, ferric, mercuric salts. | Formaldehyde. |
| | Finely powdered metals as zinc and iron. |

Of these the following require special mention—

(a) POTASSIUM CHLORATE is dangerously incompatible with any reducing agent and it should never be prescribed with sugar, glycerin, charcoal and drugs containing tannin. HYPOPHOSPHITES are particularly dangerous. These are liable to explode when simply heated or triturated vigorously in a mortar.

(b) PERMANGANATES, PEROXIDES and CHROMIC ACID are also similarly incompatible. This should always be prescribed, alone.

(c) Of the nitrite group, SPIRIT OF NITROUS ETHER is incompatible with many. Owing to its acid reaction especially when old, it should not be given with alkalies. Further, with

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| <p>23. Sp. Æther. Nitros. min. 20 Tinct. Kramer. min. 30 Aq. fl. oz. 1 (Explosive).</p> <p>24. Protargol gr. 15 Liq. Hydrog. Perox. fl. oz. 1 (Explosive).</p> <p>25. Liq. Iod. Mit. min. 60 Lin. Camph. Ammon. min. 180 (Explosive).</p> <p>26. Acid. Nitric. min. 60 Glycer. fl. oz. 1 (Explosive).</p> <p>27. Chloral. Hydr. gr. 10 Sp. Ammon. Aromat. min. 20 Aq. fl. oz. 1 (Chlorof. liberated and Chloral alcoholate formed),</p> <p>28. Dextros. gr. 60 Sod. Bicarb. gr. 15 Aq. fl. oz. 1 (Oxidation).</p> | <p>29. Pot. Chloras gr. 15 Syr. Calc. Hypophosph. min. 30 Aq. fl. oz. 1 (Explosive).</p> <p>30. Pot. Chloras gr. 30 Liq. Iod. Mit. fl. oz. 1 (Explosive).</p> <p>31. Liq. Strych. Hydrochlor. min. 8 Liq. Quinin. Ammon. min. 30 Aq. fl. oz. 1 (Strych. ppt.),</p> <p>32. Sod. Iod. gr. 10 Liq. Strych. Hydrochlor. min. 5 Aq. fl. oz. 1 (Strychnine Iodide ppt.).</p> <p>33. Quinin. Dihydrochlor. gr. 5 Sod. Salicyl. gr. 10 Aq. fl. oz. 1 (Quinine salicylate ppt.).</p> <p>34. Tinct. Nuc. Vom. min. 15 Inf. Cascarella ad. fl. oz. 1 (Strych. tannate ppt.).</p> |
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tannic acid it explodes owing to the liberation of gaseous nitrogenous compound.

NITROGLYCERIN is safe in 1 per cent. alcoholic solution but this, when diluted, deposits an explosive oily substance. This is decomposed by alkalis such as caustic potash. Glycerin explodes with nitric acid, forming nitroglycerin.

ERYTHROL TETRANITRATE should not be vigorously rubbed in the mortar for fear of explosion.

(d) IODINE forms explosive compounds with some volatile oils. It is especially dangerous with ammonia and oil of turpentine forming nitrogen iodide.

(e) CHLORAL HYDRATE, if mixed with an alkali, is decomposed to liberate chloroform; with alcohol, it forms chloral alcoholate, an undesirable compound, especially in the presence of a bromide.

(f) All monosaccharides and some of the disaccharides are unstable in alkaline solution. Glucose, levulose, galactose, maltose and lactose turn yellowish brown and smell of caramel. Stronger alkalis with heat cause the change more rapidly.

A large number of acids are produced in strong alkaline solution having 6, 5, 4, 3, 2 or one carbon atoms in them. Moreover in the absence of oxygen, volatile substances are formed which give iodoform test like ethyl alcohol and are probably glycolaldehyde, oxyacetone or glyoxal condensation products.

If air has free access or the mixture is shaken, brown colour does not appear but a rapid oxidation occurs.

3. PRECIPITATION OF ALKALOIDS—

The alkaloids (including their preparations) in the B.P. are.—Apomorphine, Atropine, Caffeine, Cinchona alkaloids, Cocaine, Codeine, Colchicine, Diamorphine, Emetine, Ephedrine, Ergometrine, Ergotoxine, Ergotamine, Hyoscyamine, Hyoscyne, Morphine, Pelletierine, Physostigmine, Pilocarpine, Strychnine, Theobromine and Theophylline. These by themselves are either insoluble or sparingly soluble in water. But by adding an acid, these are made into soluble salts and in that way these are prescribed in mixtures.

Others of therapeutic importance are aconitine, conessine, coniine, equinine, gelseminine, lobeline, nicotine and sparteine.

In all, the most important alkaloidal precipitant is an *alkali*: this precipitates free alkaloid by decomposing the salt. Further most of the alkaloids are powerful poisons and hence if prescribed with an alkali, the precipitated alkaloid settles at the bottom

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| <p>35. Quinin, Dihydrochlor. g. 5 Tinct. Rhei Co. min. 15 Aq. fl. oz. 1 (Quinin. tann. ppt.).</p> <p>36. Pot. Brom. gr. 15 Morph. Hydrochlor. gr. $\frac{1}{2}$ Aq. fl. oz. 1 (Morph. Brom. ppt.).</p> <p>37. Ferr. et Quinin. Cit. gr. 15 Pot. Iod. gr. 5 Aq. fl. oz. 1 (Quinin. Iod. ppt.).</p> | <p>38. Tinct. Colch. min. 15 Sod. Salicyl. gr. 10 Aq. fl. oz. 1 (Colch. Salicyl. ppt.).</p> <p>39. Borax gr. 15 Cocain. Hydrochlor. gr. 5 Aq. Dest. fl. oz. 1 (Cocaine ppt.).</p> <p>40. Caffein. Cit. gr. 5 Liq. Arsen. et Hyd. Iod. min. 15 Aq. fl. oz. 1 (No ppt.).</p> |
|--|--|

and the whole quantity of it may be swallowed in the last dose causing serious toxic symptoms.

Other alkaloidal precipitants are alkaline *salicylates* and *benzoates*, *bromides*, *iodine*, *iodides*, *mercuric chloride*, *picric acid* and all preparations containing *tannin*.

These sometimes may be dispensed as follows. The alkaloidal salt is first dissolved and placed in the mortar (not too much diluted) and mucilage of acacia is added. The rest of the vehicle is now gradually added with constant trituration. Caffeine citrate is incompatible with sodium salicylate, salicylic acid being precipitated : caffeine alkaloid may be used. Further several alkaloids may be dissolved in certain minute proportions (which may be near the therapeutic dose) even in alkaline solutions. *Caffeine alkaloid* may be prescribed upto 10 grains per ounce without any precipitate.

Morphine is not precipitated from 12 minims of the liquor or 9 minims of tincture of opium : *Codeine* $\frac{3}{4}$ gr. is soluble in $\frac{1}{2}$ oz. of fluid : Liquor strychnine hydrochloride will not precipitate *strychnine* upto 8 minims in an alkaline solution. Tinctures of *belladonna* and *hyoscyamus* will also not precipitate the alkaloids in their therapeutic doses. *Theobromine* and *sodium salicylate* and *Theophylline* and *sodium acetate* are alkaline in reaction and are compatible in alkaline solution but with an acid, the alkaloid is precipitated : the same happens with a bicarbonate.

Double iodide of mercury, (Mayer's reagent), precipitates all alkaloids except caffeine and theobromine.

PHYSICAL INCOMPATIBILITY

1. CHANGE OF COLOUR—

A combination sometimes forms an unsightly compound and is therefore unsuitable for dispensing.

All iron salts form an inky mixture with tannic acid. A very large number of vegetable preparations contain tannin. (See page 30). So iron should not generally be prescribed with any of these preparations. This inky solution *may be clarified* by adding a few drops of dilute phosphoric or citric acid.

Ferric salts form red colour with acetates, meconates (in opium) and salicylates : buff colour with benzoates but such

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| 41. Tinct. Rhei Co. min. 25 | Tinct. Cannabis Ind. min. 10 |
| Liq. Ferr. Perchlor. min. 10 | Aq. fl. oz. 1 (Resin is ppt.). |
| Aq. fl. oz. 1 (Iron tann. ppt.). | 47. Sod. Salicyl. gr. 10 |
| 42. Ephedrin. Hydrochlor. gr. $\frac{1}{2}$ | Sp. Æther. Nitros. min. 20 |
| Sp. Ammon. Aromat. min. 20 | Aq. ad. fl. oz. 1 |
| Aq. fl. oz. 1 (Ephedrine ppt.). | (Salicyl. acid ppt., change of colour). |
| 43. Quinin. Dibydrochlor. gr. 5 | 48. Acid. Acetyl. Salicyl. gr. 5 |
| Tinct. Digit. min. 10 | Hexamin. gr. 10 (Pasty mass). |
| Inf. Caryoph. ad. fl. oz. 1 | Sod. Salicyl. gr. 10 |
| (Quinine tannate ppt.). | 49. Liq. Ferr. Perchlor. min. 10 |
| 44. Salol gr. 5 | Aq. ad. fl. oz. 1 (Purple). |
| Camph. gr. 3 (Pasty mass). | 50. Borax gr. 10 |
| 45. Phenacet. gr. 5 | Plumb. Acet. gr. 2 |
| Chloral. Hydr. gr. 10 (Pasty). | Mucil. Acac. min. 30 |
| 46. Pot. Brom. gr. 15 | Aq. ad. fl. oz. 1 (ppt.). |

combinations are often harmless and may be admissible: if an insoluble precipitate is formed, this is suspended with compound tragacanth powder.

Spirit of Nitrous Ether is another difficult preparation. With phenazone, it gives brilliant green colour: with salicylates yellow changing to red and with resorcin, dark red. With potassium iodide, it gives yellow colour owing to the liberation of iodine unless its acidity is previously neutralised by an alkali.

Iodine causes the blue colouration with amylaceous preparations and phenolphthalein, red with alkalies.

2. CHANGE OF FORM—

In some combinations the physical properties are so altered (unless intentional), that the prescription cannot be dispensed.

Some solid preparations made together into powders are liquefied or form pasty mass. The examples are, camphor with carbolic acid, chloral hydrate or menthol. Salicylic acid (also salicylates) forms a pasty mass with boric acid, acetanilide, phenacetin or phenazone.

Acetylsalicylic acid does the same with hexamine and when sodium sulphate is combined with potassium citrate.

3. INSOLUBILITY—

Usual solvents used for making various liquid preparations are water, alcohol, glycerin, fixed oils and more rarely chloroform and solvent ether.

Water is used mostly for mineral salts, and alcohol for volatile oils and resinous substances. Glycerin is soluble both in alcohol and water and is a helpful solvent for many drugs especially for alum, boric acid, carbolic acid, corrosive sublimate and iodine. Of fixed oils, castor oil is used as solvent for many alkaloids used for the eyes as atropine, cocaine, eserine and homatropine. Olive oil and liquid paraffin are good solvents for menthol and are the basis of many liniments and throat sprays.

A soluble barbiturate forms insoluble barbitone with ammon. bromide but may be prescribed with sodium or pot. bromide.

Insoluble preparations ordered in a mixture are suspended with mucilage. This is especially necessary for many oils and oleo-resins and the preparation is called an emulsion. Mucilage of acacia is the best agent for the purpose. (See page 72).

It must be remembered, gum acacia is incompatible with alcohol, borax, iodine, iron salts, lead subacetate (form precipitate) and morphine (causes change of colour).

Therapeutic Incompatibility

Drugs having opposite actions are sometimes intentionally combined, one being the corrective of the other, as atropine is combined with morphine. But sometimes such combinations destroy or impair the activity of both or may form

compounds of altogether different action which must be avoided.

The combinations like purgatives and astringents, hypnotics and exhilarants or accelerators and inhibitors should not be prescribed without definite reasons.

SUMMARY : *Commoner precipitants may be tabulated as follows**

| | | | | Alkaloids | Heavy metals generally | Lead or Silver | Calcium | Magnesium |
|---------------------------------|-----|-----|-----|-----------|---------------------------|----------------|---------|-----------|
| Alkalies | ... | ... | ... | P | P | P | P | P |
| Tannic acid | ... | ... | ... | P | P | P | | |
| CO ₂ and Carbonates | ... | ... | ... | P | P | P | P | P |
| Sulphuric acid and Sulphates | | ... | ... | | | P | P | |
| Phosphoric acid and Phosphates | | ... | ... | P | P | P | P | P |
| Boric acid and Borates | | ... | ... | P | P | P | | |
| Hydrochloric acid and Chlorides | | ... | ... | | | P | | |
| Hydrobromic acid and Bromides | | ... | ... | P | | P | | |
| Hydriodic acid and Iodides | | ... | ... | P | | P | | |
| Sulphides | ... | ... | ... | | P | P | | |
| Arsenical solutions | | ... | ... | | P | P | | |

* Potter quoted by Hale-White.

MATERIA MEDICA AND PHARMACOLOGY

PART I

DRUGS USED MAINLY FOR LOCAL ACTION

The drugs of this group mainly *act locally* on the point of contact either on the *skin* or on the *mucous membranes* of the alimentary, respiratory or genital canal, and sometimes on the *conjunctiva*. Some of these have in addition systemic action also. The drugs acting locally are divided into several groups.

Demulcents are substances that soothe and protect certain parts of mucus membranes from irritants by their cohesive action in colloidal state. **Emollients** are substances like bland oils that soften and protect the skin from irritation. **Sweetening agents** disguise the unpleasant taste of different medicinal preparations. **Colouring agents** give an elegant appearance to drugs.

Others are **local irritants** such as volatile oils : **astringents** as tannic acid and **adsorbents** as kaolin.

Drugs having local action on the alimentary canal are more important and they are many. These act as **sialogogues**, **digestants**, **emetics** and **purgatives**. Some of these have systemic action also. These have been taken up as a separate group.

1. DEMULCENTS

Demulcents (*L. de* and *mulcere*, to soothe) are drugs of colloidal nature with local *soothing* and *protective effects* on the site of application. The drugs in this group are *gums*, *glycyrrhiza*, *amylum*, and *plantago ovata* and *pectinum*. *Gelatin* is also a demulcent but is mainly used as a basis for pastilles, jellies, bougies, suppositories and pastes.

LOCALLY, these, applied to a sensitive surface, lessen the sensation. Sugar dissolved in mucilage (as barley water) tastes less sweet and iced milk is felt less cold than iced water. **TAKEN INTERNALLY**, an irritant causes less irritation on the gastric mucous membrane in the presence of a colloid : gastrointestinal absorption is delayed : so a fluid taken with a colloid causes a greater and more persistent feeling of distension : a purgative stays longer causing better effect and an enema is more likely to be retained if a suitable colloid is present.

GUMS

1. ACACIA, (abbr. *Acac.*), *Acaciæ Gummi*, *Babla Gand.*

A dried gummy exudation from the stem and branches of *Acacia Senegal*, or other varieties of *Acacia*, in round or ovoid tears or masses of various sizes as 0.5 to 2 cm. in diameter : almost inodorous, of bland mucilaginous taste and nearly colourless, straw coloured or yellowish : contains starch and gum resin as impurities. Its chief constituent is *arabin* or arabic acid combined with calcium and to a less extent, with potassium and magnesium and is freely soluble in water making slightly acid translucent viscid solution : insoluble in alcohol (90%).

Also dispensed as a white colourless or light straw-coloured powder, *Acaciæ Pulvis*.

INCOMPATIBLES.—Ferric salts, lead subacetate, borax, sulphuric acid and dehydrated alcohol. See p. 89.

OFFICIAL PREPARATIONS.—(i) *Mucilago Acaciæ* (*Mucil. Acac.*), (p. 51) and (ii) *Pulvis Tragacanthæ Compositus* (see *Tragacanth*). Dose, 10 to 60 grains or 0.6 to 4 grammes.

2. TRAGACANTHA (abbr. *Trag.*), *Tragacanth*.

The dried gummy exudation, inodorous and nearly tasteless, in yellowish white thin flakes, tough and translucent from *Astragalus gummifer* and other varieties of *Astragalus*, is obtained from Asia Minor. It contains *Tragacanthin* which is slightly water soluble (33%) but more alcohol-soluble, *arabin-like* gum (53%) which is water soluble and also a little starch. It is partially soluble in water but swells up into a gelatinous adhesive mass.

It is prepared as colourless, angular, microscopic fragments, *Tragacanthæ Pulvis*.

OFFICIAL PREPARATIONS.—(i) *Mucilago Tragacanthæ* (*Mucil. Trag.*), (p. 51) and (ii) *Pulvis Tragacanthæ Compositus* (*Pulv. Trag. Co.*), (p. 53).

PASTA TRAGACANTHÆ COMPOSITA (B.P.C.).—*Tragacanth* powder 22.9 g., glycerin 200 ml., alcohol 95% 25 ml., phenyl mercuric nitrate 0.1 g. and water to 1000 ml. A catheter lubricant.

GLYCYRRHIZA (*Glycyrrh.*), Liquorice, *Jashthimadhu*

Dried peeled or unpeeled root and peeled subterranean stem of *Glycyrrhiza glabra* and other species of the same in unpeeled condition. Cylindrical pieces upto 2 cm. in diameter, dark brown and longitudinally wrinkled : being peeled, yellow and fibrous : faint odour and sweet taste. Obtained from India, Afghanistan, Persia, South Europe and England.

Its chief constituents are *glycyrrhizin* (a sweet amorphous glucoside), asparagin, sugar, resin, starch, gum etc.

It is also obtained as buff or yellow coloured powder of the peeled drug, *Glycyrrhizæ Pulvis*.

OFFICIAL PREPARATIONS.—*Extractum Glycyrrhizæ* (*Ext. Glycyrrh.*), Dose, 10 to 30 grains or 0.6 to 2 grammes (p. 39). (ii) *Extractum Glycyrrhizæ Liquidum* (*Ext. Glycyrrh. Liq.*), Dose, 30 to 60 minims. or 2 to 4 ml. (p. 40). (iii) *Pulvis Glycyrrhizæ Compositus* (*Pulv. Glycyrrh. Co.*), *Pulvis Pectoralis*, (p. 53). Dose, 60 to 120 grains or 4 to 8 grammes. Unpeeled liquorice is an ingredient of *Elixir Cascara Sagrada*.

AMYLUM (*Amylum*), Starch, *Moida*

Starch consists of polysaccharide granules prepared from rice and maize grains, wheat or potato and made into white, inodorous fine powder or irregu-

lar masses easily reducible to powder. Insoluble in cold water and in alcohol (95%). It is contained in *Pulvis Tragacanthæ Compositus* and is an ingredient of *Pasta Zinci Oxidi Composita*.

INCOMPATIBLE with iodine, which is turned blue.

OFFICIAL PREPARATION.—*Glycerinum Amyli* (*Glycer. Amyli*), (p. 41)
A jelly is formed by heating to about 140° and stirring.

Pharmacology [and Therapeutics]

Gums, liquorice and starch and also substances like sugar, white of egg, milk, glycerin, gelatin and fixed oils, form a viscid colloidal coating on their place of contact and have **soothing** effects on it and are called *demulcents*. A coating of mucilage on an exposed nerve end, **lessens its sensory, and reflex functions**. These are therefore prescribed for many painful conditions as inflammation in the mouth, throat, stomach or in the intestine and also for irritant poisoning. For the same reason, these are helpful in **masking the taste** of acids, sugars and of unpalatable drugs. Difference of **temperature** is less appreciated. The colloids **retard absorption** from the stomach and intestines, an irritant causing less inflammation in their presence. By diminishing absorption these tend to increase the efficiency of purgatives. These are also helpful in **adsorbing toxins** of many poisons and of infective processes.

ACACIA is most suitable for **emulsifying** the (a) fixed oils : (acacia powder one with four of the oil) and for (b) volatile oil (one in two of the oil). For suspending powders in a mixture, 10 grains of compound tragacanth powder per ounce of the mixture is more suitable (except bismuth salts which form flaky masses) and for resinous tinctures, the mucilage of acacia $\frac{1}{6}$ th of the finished mixture is required. Acacia is a suitable **pill excipient** and also occasionally used in making pastilles and lozenges.

TRAGACANTH has two fractions one soluble and the other insoluble in water and so with water, it swells up to an adhesive gelatinous mass. It is mainly used in pharmacy as a **suspending agent** in mixtures for heavy insoluble powders (especially of bismuth) and resinous tinctures and to **emulsify** volatile oils : it is unsuitable for fixed oil as the emulsion becomes thick but in some cases a combination of acacia and tragacanth answers better : an emulsion of medium thickness is obtained. See p. 72.

Tragacanth is also used in making skin cream and ointment jelly. One such preparation is *Bassorin paste* containing tragacanth 5, glycerin 2, alcohol (90%) 10 and water to 100 : may be used on the skin plain or with a non-irritating antiseptic : this is a soothing skin application. Tragacanth paste is a good **lubricant** for catheters and surgical instruments. See p. 92.

Liquorice.—The powder is sometimes used as **demulcent** for sore-throat in the form of compressed lozenges¹ and the liquid extract as a **flavouring**² to improve the taste of medicinal mixtures. But such mixture must be alkaline or neutral in reaction (p. 86). The compound powder containing senna acts as a **laxative**: this makes a colloidal compound in the intestine which by diminishing the absorption of its contents, increases the efficiency of the purgatives. It is also used as a powder or pill **vehicle**.

Amylum.—In dry form, starch is an **absorbent** and is used alone or combined with mild astringents as zinc oxide as a dusting powder for chafings and excorations of the skin. Glycerin of starch makes a jelly and is sometimes applied on chapped or cracked skin of hands as protective emollient. Starch is also sometimes incorporated into tablets as a **disintegrating** agent. This is made into mucilage and is used as a **demulcent** drink (as in the form of barley water) or as an enema mixed with Tincture of Opium for painful conditions in the rectum. Maranta or arrowroot starch gruel is more frequently used as drink in diarrhoea. Starch is an **antidote** to iodine poisoning.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

ACACIA is the dried gummy exudation from *Acacia arabic* Willd and of closely allied species.

TRAGACANTH is the dried gummy exudation from *Astragalus strobiliferus* Royle and known in commerce as Chitral gum.

These are used for the same purpose as the corresponding B.P. products.

PLANTAGO OVATA, (Spogel seeds, *Ispaghula*, also *Ispaghula testa*). This soaked in water for about 20 minutes makes a mucilaginous substance which is drunk sweetened with sugar for irritative condition in the stomach and intestine and is very useful in acute and chronic colitis. The mucilage forms a protective coating on the inflamed and ulcerated surface and soothes pain; by imbibing fluid, it increases the bulk of the fæces and ensures easy daily working of the bowels. It also adsorbs to some extent bacterial toxins. It is sometimes prescribed to relieve painful strangury of acute gonorrhoea. Two heaped tea-spoonfuls of the seeds or one tea-spoonful of the peeled cortex (husk) in 8 oz. of water, is given daily. This may be continued fairly long.

Siblin, (P.D.), the mucilaginous material of the above with vitamin B₁ in granular form is used in one tea-spoonful doses for the same purpose.

Iso-gel in granules is a mucilaginous laxative: dose, one tea-spoonful in a tea-cupful of warm water.

PECTIN, chemically allied to mucin (both containing uronic acid), often obtained from apple, forms a gelatinoid with water which taken orally in 5% solution makes a coating for an ulcerative condition in the stomach and intestine. It is used in gastro-duodenal ulcer and colitis.

Pectocel (Lilly) has in 1 fl. oz. pectin 4.5 gr., kaolin 90 gr., zinc phenol-sulphate 1½ gr., used for gastritis, enteritis and colitis.

CHONDRUS (Not official) or Irish moss in decoction is a demulcent and is also used as emulsifier for Cod liver oil. See p. 72.

- (1) $\frac{1}{2}$
Ext. Glycyrrh. gr. 3
Menthol. gr. $\frac{1}{4}$
Ol. Anis. m. $\frac{1}{3}$
Acac. q.s.
Throat lozenge.

- (2) $\frac{1}{2}$
Ext. Glycyrrh. Liq. 10
Tinct. Opii. Camph. 12
Vin. Antim. 6
Liq. Amon. Acet. Fort. 10
Aq. Dest. 100
1 to 2 fl. dr. for acute bronchitis.

2. EMOLLIENTS

Emollients (L. *E.* intensive, and *mollire*, to soften) are drugs that *soften* and protect the place of contact, either skin or mucous membrane.

The drugs in this group are (i) *Fixed vegetable oils* as almond oil, arachis oil, cotton seed oil, linseed oil, olive oil and sesame oil ; (ii) *Fats* as lard, wool fat and suet : Oil of theobroma is a vegetable fat but used as a vehicle. (iii) *Waxes* as beeswax, white and yellow also synthetic wax-like substances and (iv) *Hydrocarbons* as hard, soft and liquid paraffins.

These are used as emulsions, creams or ointment or as vehicle of certain remedies. Applied on abrasions, cuts or bruises or burns in aseptic form, these act as *protective* and by *excluding external contamination* favour healing. Being of oily nature these stay at the place of application for a longer period than a watery solution. So these make a rough skin soft and *elastic*.

FIXED OILS

1. OLEUM AMYGDALÆ, (*Ol. Amygdal.*), Almond oil. *Badam Tel.*

A pale yellow bland oil with a nutty taste and characteristic smell, expressed from *Prunus amygdalus* var. *dulcis* or *amara*, sweet or bitter almonds. It contains *olein* and *linolein*.

Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

2. OLEUM ARACHIS (*Ol. Arach.*), Arachis oil, Ground nut oil, Pea-nut oil, *China Badam Tel.*

The oil is expressed cold from the seeds of *Arachis hypogæa*, cultivated in many parts of India, China, Eastern Colonies and of Africa.

3. OLEUM GOSSYPH SEMINIS (*Ol. Gossyp. Sem.*), Cotton seed oil.

An oil expressed from the seeds of various cultivated species of *Gossypium* : yellow or pale yellow oil with bland taste and nutty or almost no smell.

4. OLEUM LINI (*Ol. Lini*), Linseed oil, *Tishi Taila*.

A yellowish brown, fixed oil expressed from linseed having the characteristic smell and bland taste. Used in the preparation of *Liquid Cresolis Saponatus*.

5. OLEUM OLIVÆ (*Ol. Oliv.*), Olive oil.

The oil is expressed from the ripe fruit of *Olea europæa* and refined.

It is a pale yellow, or greenish yellow liquid with a faint odour and bland taste. Its chief constituents are *olein*, *linolein* and *palmitin*. It is used in many liniments, ointments, plasters and in some injections. From it are made glycerin, hard and soft soaps.

If exposed to air and heat, it gradually loses colour and becomes rancid.

It is obtained from South Europe but is now being cultivated in the Himalayas and in the Nilgiris.

Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml.

6. OLEUM SESAMI (*Ol. Sesam.*), Sesame oil, *Teel Tel*.

A pale yellow oil with slight odour and bland taste expressed from the seeds of *Sesamum indicum*. Contains glycerides of *oleic* and *linoleic acids*, *stearin* and *palmitin*.

It grows in a large part of Northern India, also in Africa, Far Eastern and North American Colonies. In India and Eastern Countries, this and arachis oil may be used in the place of olive oil in making liniments, plasters, ointments and soaps. Miscible with solvent ether, chloroform and light petroleum.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

OLEUM COCOS, Cocoa-nut oil, Cocoa-nut Stearin.—This is a bland fixed oil and is largely used as emollient, hair oil and in cooking either plain or hydrogenated. It is a good bland vehicle for many drugs to be applied externally. It melts at 29°C.

OLEUM SINAPIS EXPRESSUM, Mustard oil, is the oil expressed from mustard seeds: of brownish yellow or golden yellow colour with a characteristic smell and pungent taste. This is a popular edible oil and may also be used as a liniment base.

OLEUM VEGETABILUM HYDROGENATUM, hydrogenated vegetable oil is obtained by hydrogenating a suitable oil, preferably ground nut oil or cotton-seed oil. May be used *externally* as an emollient and more extensively *internally*, for cooking.

Vegetable oil Products Controller's specification.—The hydrogenated oil should have the melting point between 31° to 37°C: fatty acids, not exceeding 0.25%: unsaponifiable matter not exceeding 1.5%: diacetyl (this gives the flavour of butter) should not exceed 6 per million: should contain at least 6% of sesame oil which makes it easily detectable by chemical test if butter or ghee is adulterated with vegetable oil product.

ACIDUM OLEICUM (*Acid. Oleic.*), Oleic acid, $C_{17}H_{33}COOH$

Prepared by the hydrolysis of fat or of fixed oils and separation of the liquid acids by expression.

A pale yellow or colourless fluid with a faint rancid smell. It darkens on exposure to air. The odour and taste also become more marked. It is insoluble in water but freely soluble in alcohol (90%), solvent ether, chloroform or in benzene.

Oleic acid is an ingredient of *Hydrargyrum Oleatum* and *Injectio Æthanolaminæ Oleatis*.

ÆTHYLIS OLEAS (*Æthyl. Oleas*), $C_{20}H_{38}O_2$.

Ethyl oleate is prepared by esterification of oleic acid with ethyl alcohol: should have 98% w/w of the active substance. A pale yellow oil with strong and disagreeable odour and taste. Insoluble in water: miscible with vegetable oils.

FATS

1. ADEPS (*Adeps*), Prepared lard, *Sukar Charbi*.

It is a soft, white, unctuous fat, obtained from the internal fat of hog, *sus scrofa*. Insoluble in water, very slightly soluble in alcohol (90%), soluble in solvent ether, chloroform and in light petroleum.

It contains 60% of *olein* and the rest, *stearin* and *palmitin*.

Lard is an ingredient of *Unguentum Hydrargyri Nitratis Forte* and *Unguentum Phnolis*.

OFFICIAL PREPARATIONS.—**Adeps Benzoinatus** (*Adeps Benz.*), See p. 36.

As lard becomes rancid on keeping, benzoin is added as a preservative. Suet may be used for lard.

2. ADEPS LANÆ (*Adeps Lan.*), Wood fat, Anhydrous lanolin.

Purified fat-like substance obtained from sheep's wool. It is a yellowish, tenacious, almost inodorous unctuous substance melting at about 40°. Insoluble in water, slightly soluble in cold alcohol (90%) but freely in solvent ether and chloroform.

Wool fat is an ingredient of *Unguentum Hamamelidis* and *Unguentum Hydrargyri*.

OFFICIAL PREPARATIONS.—(i) *Adeps Lanæ Hydrosus* (*Adeps Lan. Hydros.*), See p. 36. (ii) *Unguentum Simplex* (*Ung. Simp.*), Simple ointment. See p. 63.

3. ALCOHOLIA LANÆ (*Alcoh. Lan.*), Wool Alcohols.

It is prepared by saponification of fat obtained from wool of sheep and separating the fraction containing cholesterol and other alcohols. It contains not less than 28% of Cholesterol.

It is a golden brown solid having a faint but characteristic odour, somewhat brittle when cold becoming plastic when warm.

It is insoluble in water, freely soluble in solvent ether and chloroform and moderately soluble in alcohol 90%.

OFFICIAL PREPARATIONS.—(i) *Unguentum Alcoholium Lanæ* (*Ung. Alcoh. Lan.*), Ointment of wool alcohols and (ii) *Unguentum Aquosum* (*Ung. Aquos.*), Hydrous Ointment. See p. 62.

SEVUM (*Sev.*), Prepared Suet. (*Not official*).—Is the purified abdominal fat of sheep, *Ovis aries*. It contains about 30% of olein and the rest are palmitin and stearin : may be used for lard.

SOAPS

These are sodium, potassium, calcium, ammonium or magnesium salts of palmitic, stearic or oleic acids. The following are in the B.P.

1. SAPO ANIMALIS (*Sap. Animal.*), Curd soap.

Animal or Curd Soap made by the interaction of purified solid animal fats with sodium hydroxide, caustic soda, is nearly inodorous yellowish white or greyish white substance. It is mostly sodium stearate. Soluble in alcohol (90%) and hot water but sparingly soluble in cold water.

Curd Soap is an ingredient of *Extractum Colocynthis Compositum*.

2. SAPO DURUS (*Sap. Dur.*), Hard soap, Castile soap.

Hard Soap is made by the action of caustic soda on olive oil or any other suitable vegetable oil or fatty acids derived therefrom : cocoanut or palm kernel oil is not admitted. It is a greyish white or yellowish white substance ; nearly odourless and when dry, becomes horny and pulverisable : soluble in 20 parts of cold and 1.5 parts of hot water : almost completely soluble in alcohol (90%).

Hard Soap is an ingredient of *Unguentum Zinci Oleatis*.

3. SAPO MOLLIS (*Sap. Moll.*), Soft soap, Green soap.

It is prepared by the action of caustic potash or caustic soda on any other suitable vegetable oil or oils or fatty acids derived therefrom : cocoanut or palm kernel oil is not admitted. It is a yellowish white or greenish unctuous substance, soluble in water and alcohol (90%). It contains not less than 44% of fatty acids.

Soft Soap is an ingredient of *Linimentum Terebinthinæ*.

OFFICIAL PREPARATION.—*Linimentum Saponis* (*Lin. Sap.*), OPODELDOC, See p. 48.

WAX

1. CERA FLAVA (*Cera Flav.*), Yellow beeswax, *Mom.*

This is obtained from the honeycomb of the bee, *Apis mellifica* or other species of *Apis* in India and other countries. A yellowish brown solid substance, insoluble in water, slightly soluble in alcohol (90%), more in solvent ether and chloroform and in fixed and volatile oils. This has a faint honey like odour; somewhat brittle when cold and on warming, becomes plastic.

2. CERA ALBA (*Cera Alb.*), White beeswax.

This is made by bleaching yellow beeswax, yellowish white, translucent solid substance with a faint characteristic smell.

These are in INDIAN PHARMACOPŒIAL LIST also.

WAX-LIKE SUBSTANCES

1. ALCOHOL CETOSTEARYLICUM (*Alcoh. Cetostearyl.*).

Cetostearyl Alcohol is a mixture of solid aliphatic alcohols, chiefly stearyl and cetyl alcohols, obtained by reduction of appropriate fatty acids or from sperm oils.

White or cream coloured unctuous mass or almost white flakes or granules: when heated, melts to a clear colourless or pale yellow liquid; has a faint characteristic odour and bland taste.

This is an ingredient of *Cera Emulsificans*.

2. SODII ET LAURYLIS SULPHAS (*Sod. et Lauryl. Sulph.*).

Sodium Lauryl Sulphate is a mixture of normal primary sodium alkyl sulphates consisting chiefly of sodium lauryl sulphate. It contains not less than 58% w/w of total alcohols.

White or pale yellow powder or crystals with slight but characteristic odour. Soluble at 15.5°, in 10 parts of water making an opalescent solution: slightly soluble in alcohol 90%.

It is an ingredient of *Cera Emulsificans*.

CERA EMULSIFICANS (*Cera Emulsif.*).—Emulsifying wax contains cetostearyl alcohol 90 g., sodium lauryl sulphate 10 g. or similar sodium salts of higher primary aliphatic alcohols and distilled water 4 ml.

Cetostearyl alcohol is melted at 95°, sodium lauryl sulphate and distilled water added and heated to 115°: stirred vigorously and cooled quickly. Almost white or pale yellow waxy solid, becoming plastic when warm. Odour is faint and characteristic. Almost insoluble in water forming an emulsion: moderately soluble in alcohol (95%).

Used in the preparation of *Ung. Emulsif.*, *Ung. Emulsif. Aquos.* (p. 62), *Cremor penicillin.* and *Cremor penicillin. steril.* (p. 37).

Lanette Wax SX (Not official) is a mixture of 90 parts of stearyl and cetyl alcohols together with 10 parts of sulphates and phosphates of these alcohols. This can emulsify many times its own weight of aqueous liquids and so a wide range of oil-in-water type of emulsions may be prepared with it.

PARAFFINS

1. PARAFFINUM DURUM (*Paraff. Dur.*), Hard paraffin.

It is a mixture of solid hydrocarbons obtained from petroleum and from shale oil; a colourless or white, inodorous, tasteless, translucent mass, often showing a crystalline structure, freely soluble in solvent ether and chloroform and sparingly in alcohol (90%) but not in water. Burns with a luminous flame.

This is an ingredient of *Unguenta Alcoholium Lanæ, Paraffini, Phenolis* and *Simplex*.

2. PARAFFINUM MOLLE (*Paraff. Moll.*), Soft paraffin, Vaseline.

This is a greasy, white or yellow (*Paraffinum Molle Album* or *Flavum*), semi-solid substance and slightly fluorescent: obtained from petroleum: not acted on by acids, alkalies or oxidising agents and unlike animal fat, does not become rancid.

White Soft Paraffin is an ingredient in *Unguenta Alcoholium Lanæ*, *Emulsificans*, *Hydrargyri*, *Paraffini*, *Phenolis*, *Simplex* and *Zinci Oleatis*.

Yellow Soft Paraffin is an ingredient of *Unguenta Alcoholium Lanæ*, *Dithranolis*, *Hamamelidis*, *Hydrargyri Nitratis Dilutum*, *Paraffini* and *Simplex*.

3. PARAFFINUM LIQUIDUM (*Paraff. Liq.*), Liquid paraffin.

This is a tasteless, colourless and inodorous bland oily liquid having the sp. gr. of 0.865 to 0.895. It is a mixture of liquid hydrocarbons obtained from petroleum.

DOSE, $\frac{1}{4}$ to 1 fl. oz. or 8 to 30 ml.

Liquid Paraffin is an ingredient of *Unguenta Alcoholinum Lanæ* and *Emulsificans*.

OFFICIAL PREPARATION.—**Emulsio Paraffini Liquid** (*Emuls. Paraff. Liq.*). Emulsion of Liquid Paraffin. See p. 38.

DOSE, $\frac{1}{4}$ to 1 fl. oz. or 8 to 30 ml.

4. PARAFFINUM LIQUIDUM LEVE (*Paraff. Liq. Lev.*), Light liquid paraffin.

This is a mixture of liquid hydrocarbons obtained from petroleum. A transparent, colourless almost inodorous oily liquid without fluorescence by day light, insoluble in water and alcohol (90%) but soluble in solvent ether, chloroform and in fixed and volatile oils.

GLYCERINUM (*Glycer.*), Glycerin, glycerol, $C_3H_8O_3$

It is prepared by the hydrolysis of fats and fixed oils, by their interaction with alkalies or super-heated steam. It is a trihydric alcohol. It contains not less than 98% of $C_3H_8O_3$.

It is a clear, sweet syrupy hygroscopic liquid, with no colour or smell. It mixes well with water and alcohol (90%) but not with chloroform, solvent ether or fixed oils.

Glycerin is an ingredient of *Cataplasma Kaolini* and *Gelatinum Zinci*.

OFFICIAL PREPARATIONS.—(i) **Glycerinum Acidi Borici** (*Glycer. Acid. Boric.*), Boroglycerin Glycerite. (ii) **Glycerinum Acidi Tannici** (*Glycer. Acid. Tann.*). (iii) **Glycerinum Amyli** (*Glycer. Amyl.*). (iv) **Glycerinum Boracis** (*Glycer. Borac.*) and (v) **Glycerinum Phenolis** (*Glycer. Phenol.*), See p. 41. If applied locally, it should not be diluted with water which will make it corrosive. (vi) **Suppositorium Glycerini** (*Supp. Glycer.*), each suppository containing 70% of glycerin. See p. 55.

This must be wrapped with wax paper when dispensed as it absorbs moisture and softens.

GLYCERINUM PEPSINI (Not official).—Pepsin 100, hydrochloric acid 11.5, glycerin 600, distilled water to make 1000. One fluid dr. contains $5\frac{1}{2}$ gr. of pepsin.

DOSE, 60 to 120 minims or 4 to 8 ml.

Pharmacology [and Therapeutics]

The Emollients (*L. emollire*, soften) are divided into four groups: *vegetable oils*, *fats*, *waxes* and *hydrocarbons*.

Their GENERAL ACTION, *externally* on the place of application is soothing and softening and often protective.

Taken Internally, these have the same **soothing** action and relieve irritation in the gastro-intestinal tract and the first and second groups have also a food value. In bigger doses, these act as **purgative** and for this, liquid paraffin is more preferable. These in addition, **diminish the acid secretion** of the stomach.

FIXED OILS

The fixed oils are not only used as **emollients** to a raspy or inflamed skin surface, but also as **vehicles** for various external applications. The stratum corneum or the superficial layer of the skin is not permeable to water or other liquids and absorption of any drug may take place from the skin, only through its glandular structures. As the openings are filled with sebum, a fatty matter, any drug in fat or fat soluble basis can be made to enter through these and be absorbed. Therefore these fixed oils are used as basis of drugs meant to be absorbed through the skin. A part of the fat, so entered, has slight **nutritive value**.

These also act as **protective** to ulcers and abrasion and are applied either plain or with an antiseptic as ointments. The main action is one of a sterile soothing covering over an open wound excluding bacteria from outside.

OLIVE OIL, OLEIC ACID.—Olive oil is used as an **emollient** and (a) soothing application in various skin diseases characterised by roughening or increased sensitivity of the skin : (b) as **vehicle** of liniments and is also rubbed into the skin to be absorbed and (c) act as a **food**.

Oleic acid more easily penetrates through the skin when rubbed [and so it is used as a basis of ointment meant for absorption especially those of metallic oxides and of alkaloids].

ETHYL OLEATE is the *solvent* for all oil-soluble injectibles in the Pharmacopœia. (See p. 43).

Taken internally, olive oil acts as a **demulcent** [and is useful in irritant poisoning as by phenol]. It **reduces excessive acid secretion** of the stomach³ [and so it is often given internally in gastric ulcer in $\frac{1}{2}$ to 1 fluid oz. doses 3 times daily after food. It protects the ulcer from irritation and absorbed portion of the oil acts as a food]. In a larger dose as 1 to 2 fluid oz., it is a mild laxative and is given orally or 2 to 4 oz. of it made into an *enema*, plain or emulsified with 1 to 2 pints of soap solution, is useful in removing hard scybala from lower bowels. The oil absorbed from the alimentary tract acts as **food**.

Cholesterin of **gall-stone** is soluble in olive oil or oleic acid outside the body. Olive oil in 3 to 6 oz. doses and if this is not tolerated, oleic acid 2 c.c. (in $\frac{1}{2}$ c.c. capsules), is sometimes

(3) R

Ol. Oliv. fl. oz. 2

To be given at bed-time in gastro-duodenal ulcer.

For gall-stone, $\frac{1}{2}$ fl. oz. t.d. before food or 4 fl. oz. at bed-time.

given orally for this condition. Often there is relief of symptoms but the mode of action is unknown. Introduced into the duodenum with Einhorn's tube, the oil causes contraction of the gall-bladder, emptying its contents. Perhaps, the same also happens when oil is taken orally and is therefore prescribed for **cholecystitis** (inflammation of the gall-bladder). The unhealthy bile is drained out relieving pain and other symptoms of disease.

Olive oil is used as a **solvent** for ether or paraldehyde given per rectum for anaesthesia and for several fat-soluble drugs given by intramuscular injection.

ARACHIS OIL and **SESAME OIL** are generally used in making liniments and as **vehicle** of many oil-soluble drugs made into injections. Sesame oil, mixed with perfumes, is made into popular hair oil. Both are also used for cooking either plain or hydrogenated.

The ground nuts are eaten, being a nourishing food, containing about 25% protein, 38% fat and 24% carbohydrate (MacCarrison).

ALMOND OIL and **LINSEED OIL** are also used as **demulcents** and **emollients**. Almond oil is pleasanter but is more expensive. This is made into hair oils and is sometimes given orally or per rectum (enema) as a **laxative**. Being moderately penetrating through the skin, drugs are dissolved in it to make liniments for the absorption, by counterirritation, of deep seated inflammatory products. This is also used in the preparation of cold creams and other toilet articles.

Sweet almond is a good article of food and on account of its high fat and low carbohydrate contents, it was one time considered a helpful food in diabetes mellitus.

COTTON SEED OIL is a cheap substitute for Olive oil and is emollient externally and demulcent internally. This with arachis and sesame oils is the constituent of most brands of the hydrogenated oils (p. 96).

FAT AND WAX

Adeps and **lard**, prepared suet, anhydrous or hydrous **wool fat** and **wool alcohols** from sheep's wool, **cera alba** or **flava** are all used as basis for ointments.

LARD is now less commonly used: of the 25 official ointments only two are prepared with it (p. 62) and the rest, with paraffins, wool fat, wool alcohols and beeswax: zinc oleate ointment has hard soap shavings with paraffin. Lard is unpleasantly greasy, not as readily available in large quantity and tends to turn rancid: benzoinated lard keeps well and is suitable except when benzoin is incompatible as in strong mercuric nitrate ointment. All fats (animal and vegetables) penetrate the skin.

WOOL FAT can take about 30% of water making water-in-oil emulsion: This is cooling, emollient and may be vehicle

for absorption of certain medicines through the skin: it also makes toilet creams.

WOOL ALCOHOL is a better emulgent and is frequently used for making ointment creams.

Hydrous ointment is a good example of "Cold cream". When applied on the skin, the water in it evaporates withdrawing heat from the skin, producing cooling action: fat is left to be absorbed slowly causing prolonged emollient action on the superficial layers of the skin.

BEESWAX with paraffins makes emollient ointments and sometimes used to raise the melting point of suppositories. It is used in the oily injections of penicillin: its important constituent *myricin* being absorption-delaying, such injections are slowly absorbed causing sustained action.

CETOSTEARYL ALCOHOL AND SODIUM LAURYL SULPHATE.—These make synthetic esterified wax emulsions now largely used as basis for water-soluble creams and ointments. (See p. 75) The secretion of the normal healthy skin is neutral and creams formed with these are also neutral. Penicillin cream is the typical example.

The SOAPS are sometimes used as **vehicle** for pill masses and plasters (hard soap p. 77) or liniments (soft soap: this increases the penetrability). Soaps are mild **laxatives** but these are not administered orally. One ounce of soft or hard soap dissolved in 1 to 2 pints of warm water, is often used alone or with castor oil as an **enema**. This is particularly useful if there are hard impacted faecal masses in the lower bowels. A cone made of hard soap is used as suppository for children.

Soaps are more largely used as **detergents** for cleansing purposes. In contact with water these liberate some alkalis which act on the superficial fat of the skin and in this way remove superficial dirt, epithelia, scales and scabs from the skin [and hence are essential necessities in health and in diseases especially of the skin].

Soaps are weak **disinfectants** and are attempted to be made stronger by combining with an antiseptic (such as carbolic soap) although both penetrability and disinfective power of the latter are much reduced in such a combination. These are also used in alcoholic or ethereal solutions for the same purpose.

Non-official Preparations

STEARIC ACID, a mixture of solid fatty acids is sometimes used as a substitute for wax in ointments: as lubricant in making compressed tablets: partly neutralised, it forms with water a creamy base for varnishing creams.

CETYLTRIMETHYLAMMONIUM BROMIDE, *Cetrimide* or *Cetavlon*, a white inodorous powder, readily soluble in water making a neutral or slightly alkaline solution. A 1% solution is a cationic **detergent and antiseptic** and used for preoperative disinfection of the skin, in skin diseases for removal of the dirt, scabs and crusts and for disinfection of surgical instruments and utensils.

ETHER SOAP.—Soft soap 32, alcohol (90%) 20, mixed kept for 24 hours and methylated ether to 100.

SYNOL SOAP.—Liquid soap containing cresols about 2½%.

PARAFFINS

These are higher carbons of the methane series left after more volatile constituents of petroleum have been distilled over. The lower ones of this series are liquid.

(1) **LIQUID PARAFFIN**.—This is sometimes used as a **soothing** dressing and **protective** to superficial ulcerative conditions especially of burns. It is also useful in skin diseases for the removal of desquamating crusts. It is a useful catheter lubricant.

Taken internally, it is neither decomposed nor absorbed from the intestine unless taken continuously for a long time : it simply adds to the bulk of the fæcal matter and softens it and therefore acts as a helpful lubricant and **non-irritating laxative** [It is frequently used with benefit in chronic constipation and also in conditions where an evacuation is necessary without exciting much peristalsis of the intestine, as in anal fissure and painful piles].

But the disadvantages are that it sometimes fails to empty the bowels properly, takes a long time to start action and sometimes the oil, separated from fæcal matter, leaks through. Some people find the taste nauseating. [It is given in half ounce doses, 2 to 3 times a day or 1 to 2 oz. as a single dose at bed-time preferably in an emulsified form* with agar: This mixes more freely with fæcal matter and is more certain in action but sometimes hampers digestion]. Prolonged administration may retard the absorption of fat soluble vitamins especially vitamin A.

EMULSIO PARAFFINI LIQUIDI CUM AGAR (B.P.C.).—Liquid paraffin 5 fl. oz., agar 33 gr., acacia powder $\frac{1}{4}$ oz., tragacanth powder 11 gr., sodium benzoate $7\frac{1}{2}$ gr., vanillin $2\frac{1}{4}$ gr., oil of lemon 5 min., glycerin $\frac{1}{2}$ fl. oz. and water to 10 fl. oz.

(2) **LIGHT LIQUID PARAFFIN** being of low viscosity is more suitable for use as a spray for the throat and nose : the spray apparatus more readily atomizes it : it dissolves menthol (1 in 8), also cocaine, ephedrine and volatile oils, the usual ingredients.

(3) **HARD PARAFFIN** is mixed with oils and fats of low melting point to make **ointment basis**. Melted paraffin is used as a protective to clean abrasions, burn or over sprains also injected subcutaneously to restore the shape of certain parts after plastic operation.

(4) **SOFT PARAFFIN** (vaseline).—This is an **emollient** for hard rough skin and applied on the hair as a **pomade**. This is a non-irritating ointment basis which is not acted on either by acids or alkalies or by any powerful oxidising agent and does

* Angier's Emulsion and Petromulsion : (Paraffin with hypophosphites). Paragol, Parolax, Petrolagar and Agarol : (Paraffin with agar agar or phenolphthalein or both). Also prepared with cascara sagrada (Petrolagar with cascara) and with mag. carb. (Cremaffin).

not become rancid; so it can be used with a variety of medicines, making it practically the **universal ointment basis**. As it is not very much absorbed through the skin, it is made up with wool fat and wool alcohols which make it more absorbable and such a combination is now more often used and is good vehicle. It is an antiseptic and preservative.

GLYCERIN

Glycerin is a **solvent** for many drugs as iodine, bromine, boric acid, tannic acid, many metallic salts and alkaloids. It readily penetrates through the skin and does not rapidly evaporate. So a drug dissolved in it remains in contact for a long time and gets chance to be absorbed⁴. It is the *basis* of some of the toilet creams. It thus acts as a local **demulcent** protective. [It is used for many painful and inflammatory conditions either in the skin or in the mouth, throat, ear or cervix uteri]. Applied undiluted, owing to its lymphogogic action, it absorbs water and is therefore astringent and a helpful **resolvent** of a localised exudate. A paste made with magnesium sulphate is frequently used in cellulitis and carbuncle. [It is applied to various inflammatory surfaces in the skin or mucous membrane to reduce a local congestion as paste, paint, tampon of gauze soaked in glycerin or this is applied mixed with kaolin as in Cataplasma kaolini].

It is **slightly irritant** to the mucous membranes. It is frequently used as an **enema**: $\frac{1}{2}$ to 1 fl. oz. of it, plain or diluted with warm water or along with olive oil⁵, is given for emptying the lower portion of the colon. It acts promptly by withdrawing fluid from the rectal mucous membrane which starts peristalsis and seldom fails to act. A single motion follows without any after-effect. A suppository is often sufficient for a child.

TAKEN INTERNALLY, it is sweet and is used as a **flavouring** to mixtures, especially of astringent drugs, like iron. It is also used in linctuses and pastilles. In a bigger dose, as 60 to 120 minims, it acts as a **purgative**. It is readily absorbed from the intestine, oxidised in the system and acts as a **food**. A small portion is excreted in the urine and like sugar, reduces Fehling solution.

3. SWEETENING AGENTS

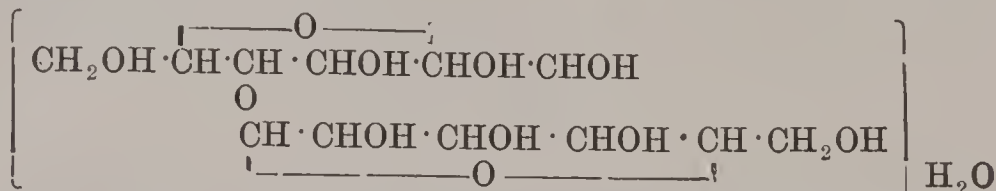
This group includes *sucrose, glucose, dextrose, levulose, lactose, purified honey, malt extract, saccharin* and *soluble*

(4) R
Ichtham. gr. 60
Ext. Bellad. Liq. m. 20
Ext. Opii Sicc. gr. 20
Glycer. ad. fl. oz. 1
To apply on a painful part.

(5) R
Oleum Ricini 2
Glycerinum 4
Oleum Olivæ 6 (Cohens, Gittens)
To be given per rectum in faecal
impaction.

INCOMPATIBILITY.—Usual oxidising agents and also alkalis. (It is worth remembering that *sodium bicarbonate* is incompatible with *glucose* and *lævulose* in solution, decomposition and oxidation taking place). See p. 87.

6. **LACTOSUM** (*Lactos.*), Lactose, Saccharum Lactis, Sugar of Milk, $C_{12}H_{22}O_{11}H_2O$.



White, inodorous crystalline powder, prepared from the whey of milk. It is a crystalline disaccharide consisting mainly of alpha and less so of beta-lactose : is faintly sweet and often gritty : soluble in 7 parts of cold and in 1 of hot water : almost insoluble in alcohol (90%).

7. **MEL DEPURATUM** (*Mel. Depur.*), Purified honey, *Madhu*.

Thick yellowish syrupy liquid, with characteristic smell and sweet taste, becoming crystalline on keeping. Commercial honey is heated in water bath and while still hot, is strained through warm flannel.

It contains mainly *glucose* and *lævulose* and has a characteristic odour with a sweet and faintly acid taste.

OFFICIAL PREPARATIONS.—**Oxymel.** See p. 51.

DOSE, 30 to 120 minims or 2 to 8 ml.

Honey is used in the preparation of *Oxymel Scillæ*.

8. **EXTRACTUM MALTI** (*Ext. Malt.*), Extract of Malt.

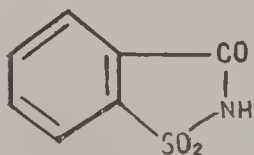
Sound malted barley seeds (*Hordeum distichon*) or a mixture of this with not more than 33% of sound malted grain of wheat (*Triticum sativum*) are first allowed to germinate : this is digested with water and then dried. A starch splitting ferment, *diastase* is present in the germinating seed which converts starch into maltose. Malt is the watery extract of these substances.

It is an amber coloured viscous fluid with an agreeable odour and sweet taste. It contains *maltose*, *dextrin*, *diastase* and *vitamin B₁* and 4% protein nitrogen.

DOSE, 60 to 1 fl. oz. or 4 to 30 ml.

Preparation : *Extractum Malti cum Oleo Morrhue*.

9. **SACCHARINUM** (*Saccharin.*), Gluside, Benzosulphimide, $C_7H_5O_3NS$.



Saccharin is *o*-benzoic sulphimide and prepared by oxidation of *o*-toluene sulphonamide : contains not less than 97% of $C_7H_5O_3NS$.

White crystals or crystalline powder, inodorous or faintly aromatic with intensely sweet taste.

Soluble at 25° in 290 parts of water and in 31 parts of alcohol (95%) : slightly soluble in chloroform and solvent ether.

10. **SACCHARINUM SODIUM** (*Saccharin. Sod.*), Soluble Saccharin, $C_7H_4O_3NSNa, 2H_2O$.

Prepared by the action of sodium hydroxide or sodium bicarbonate on Saccharin (*o*-benzoic-sulphimide). An intensely sweet, white crystalline powder, soluble, in 1½ of water and in 50 of alcohol (95%).

INDIAN PHARMACOPŒIAL LIST

1. **MALTUM** (*Malt*) is the grain of one or more varieties of cereals as barley, wheat and cholam partially germinated artificially.

(a) **EXTRACTUM MALTI** is obtained by extracting Malt with water at 60° and mixed with 10% by weight of glycerin.

(b) **EXTRACTUM MALTI CUM OLEO SELACHOIDEI** contains approximately 5% w/v sharkliver oil and not less than 200 units of vitamin A per gramme.

Dose, 60 to 240 minims or 4 to 16 ml.

2. **MEL** or **HONEY** is obtained from honey comb of bee either by draining or submitting the honey-comb to pressure.

Pharmacology [and Therapeutics]

CANE SUGAR

Cane Sugar is used mostly as a **sweetening agent** for making nasty drugs palatable. For this purpose it is made into various syrups and added to medicinal mixtures. It is also a **demulcent** [and is frequently made into linctus for irritable throat cough].

Sugar is of great **food-value** being the most readily oxidisable of all food-stuff and is an essential article of food. A concentrated syrup resists fermentation owing to its higher osmotic tension and is therefore used as a **preservative** for various pharmaceutical preparations. It is a **mild diuretic**, increasing the secretion of urine by causing, when absorbed, a temporary hydræmia of the blood, greater escape of fluid into the renal tubules and less tubal reabsorption. A sugared drink is a **mild laxative** acting probably by delaying absorption of fluid. But if taken in excess or too concentrated, it causes nausea, vomiting and diarrhœa.

Highly concentrated sucrose as 50% solution given intravenously in 50 c. c. dose is a **powerful diuretic** as this is not metabolised in the blood and the kidneys treat this as a foreign body for the purpose of excretion and tubal reabsorption is insignificant. But in animal experiment, this has caused renal damage (Anderson and Bethea, 1940) and so should not be used as freely for therapeutic use as dextrose solution.

GLUCOSE, LÆVULOSE, LACTOSE

Glucose and Lævulose being monosaccharides, are absorbed direct from the alimentary canal without requiring previous digestion. Lactose is converted into glucose and galactose by *lactase* of succus entericus in the intestine. Being readily absorbed, these are more suitable for administration by mouth as **food** in many diseased conditions with impaired digestion than cane sugar : especially suitable when quicker concentration of glucose in the blood is necessary. Glucose is largely prescribed in many conditions of **toxaemia** where food assimilation is poor and also in **ketosis** (acidosis from incomplete combustion of fat and protein) along with insulin by injection. This is a **diuretic** also, increasing the flow of urine : but as glucose is readily removed from the blood, stored as glycogen and does not reach the kidneys sufficiently, unless given in a very big dose as 50% solution 50 c.c. intravenously, this action is not sufficiently marked.

Glucose is frequently prescribed in many acute or chronic infective processes where both nourishment and free urination are required [as in severe vomiting and diarrhoea, especially in toxæmia of pregnancy, cyclic vomiting and travel sickness; pneumonia, typhoid fever or acute nephritis.

GLUCOSE.—Syrup of liquid glucose is a good **pill excipient**. Liquid glucose is suitable for oral and rectal administration only. An ounce of glucose, diluted with 10 oz. of water is often given 3 to 4 hours before chloroform or tribromoethyl alcohol anæsthesia or before an intravenous injection of arsenic or antimony compounds. Glucose is also useful during treatment with cinchophen and carbon tetrachloride which are toxic to the liver. The liver having a good supply of glycogen, gets protection.

Dextrose is given by *rectal, subcutaneous, intramuscular and intravenous routes*. [For the rectal and subcutaneous administration, an *isotonic solution* (5%) should only be chosen and are indicated in many conditions where not only glucose but also a free supply of water is necessary as in many acute infective fevers, surgical shock, tissue dehydration following severe vomiting and purging and various intoxications. About one pint at a time and a total of 2 pints or more of such a solution may be given in 24 hours. Sodium chloride is also often required which may be 60 to 90 grs. per pint of the solution. A slow continuous drip is a good method of administration.

Protein hydrolysate with 5% glucose is given intravenously very slowly in a condition of hypoproteinæmia and collapse from starvation and is often helpful: repeated every 3 or 4 days. Allergic reaction may occasionally appear.

For *intramuscular injection*, 12.5% solution is usually chosen. The advantage is that it may be given easily, a sterilized solution being available in the market. But not more than 50 c.c. can be given at a time which even is accommodated by tearing some muscular fibres and being hypertonic also, causes pain and the absorption is slow.

For *intravenous injection*, 5 to 50% solution is usually chosen, more diluted ones being preferred where fluid is also required and may be administered in slow drip. But for such conditions as ketosis, toxæmia of pregnancy, obstinate oedema or raised intracranial pressure, a concentrated solution in small bulk is preferred as 50% solution 50 c.c..

Both hypertonic glucose and saline solutions attract a large volume of fluid into the circulation but being less mobile than sodium chloride, glucose keeps up this hydræmia for a longer period and so is more effective in cerebral oedema.

When glucose in hypertonic solution is required to be given intravenously, condition of the cardio-vascular system should be carefully considered. Given in a condition of myocardial failure, on account of osmotic disturbance, there may be alarming symptoms and even fatality. Further, in all cases, it should

be injected very slowly. Introduction of glucose into the blood induces liberation of insulin from the pancreas. If a large amount of glucose is suddenly thrown in, so much of insulin may be poured out that there may be hypoglycæmic shock.

LACTOSE being less sweet than glucose or cane sugar, can be given by mouth in greater concentration : 10% solution may be easily given. It is a **mild laxative** and therefore sometimes causes looseness of the bowels. Very few of the pathogenic intestinal bacteria act on it : so it is better tolerated in certain intestinal diseases. It is often added to **cow's milk** in infant feeding to **humanise** it (that is to say to raise its sugar value equaling that of human milk), about 2.5% of it being usually required. Cow's milk contains about 4.5% and human milk 6.5% of lactose. It is **non-hygroscopic** and is a good powder-vehicle and diluent.

LÆVULOSE is a stronger sweetening agent than cane sugar, more easily assimilated and has a good flavour. It is readily oxidised and is better suited in diabetes mellitus. It is also more useful in many wasting diseases. Cane sugar or glucose, given by the mouth raises the blood sugar level but this does not happen with lævulose, provided the liver is healthy. Therefore, if 50 grm. of lævulose is given on empty stomach in the morning and blood sugar is estimated every half hour for two hours, it should not go above 0.14%, provided there is no deficiency of the liver function. (*Liver efficiency test*).

SUMMARY.—**Sucrose** is a food, sweetening agent, preservative and mild laxative. **Liquid Glucose** is readily assimilated and is given orally as food and **Dextrose** in 5% solution subcutaneously or per rectum, in 12½% solution intramuscularly and in 5% to 50% solution intravenously for tissue nourishment, ketosis, toxæmia and to cause diuresis : in a state of collapse, 5% dextrose with 0.9% sodium chloride (also adrenaline chloride solution), 1 to 3 pints, may be given intravenously : protein hydrolysate is added to it in a case of starvation. **Lactose** is used orally only when glucose cause fermentation and added to humanise cow's milk. **Lævulose** is seldom used therapeutically, except for liver efficiency test.

MEL DEPURATUM (Purified honey)

This has got **nutritive** value of sugars and is an article of diet with certain people : may be added to diet of infants suffering from bowels diseases. It is also prescribed for its **soothing** and **flavouring** properties. It makes good **cough linctus** and mel boracis is a favourite application for stomatitis. It is, in addition, a **laxative** and is given to children for that purpose.

MALT EXTRAT

This is not only a **palatable** and easily assimilable carbohydrate food, suitable for many wasting diseases especially pulmonary tuberculosis, the diastase present in it, makes it a

helpful **digestive agent** of other carbohydrates in the food. It contains a certain amount of **vitamin B₁**.

It is often combined with Cod Liver Oil or vitaminised oil as a **flavouring** to be taken after food. It is a suitable ingredient of many invalid food.

MALTOSE is beta-glucose-4-alpha-glucoside obtained from starch hydrolysed by enzyme diastase: used as a bacteriological culture medium. DEXTRI-MALTOSE (powder containing maltose 51%, dextrin 42%, without salt or with either 2% sod. chlor. or 3% pot. bicarb.) and MALTO-DEXTIN (50% maltose, rest dextrin and malto-dextrin) are added to milk and other invalid food: easily digestible and nourishing.

SOLUBLE SACCHARIN

Although like other benzoic acid preparations it is also an **antiseptic**, it is not used as such. Its main use is as a **sweetening agent** being about 500 times sweeter than cane-sugar. Even 1 in 70,000 solution in water tastes sweet and 1 in 2000 solution is sufficiently flavouring. It has a popularity among the diabetics who cannot take sugar. But unlike sugar, it is of **no food-value** and if taken for a long time, it may upset digestion. Sodium saccharin 2.5 grammes in 4 millilitres of warm water for injection has been used for measuring the arm to tongue **circulation time**. In a normal person, in 9 to 16 seconds after injection into the median basilic vein, a sweet taste is obtained: this is delayed in congestive heart failure, may exceed 45 seconds.

4. COLOURING AGENTS

Coccus (*Cocc.*), Cochineal, *Crimidana**

Cochineal is the dried fecundated insect, *Dactylopius coccus*. This is plano-convex or oval in outline and purplish black or purplish grey in colour, size, 3.5 to 5.5 mm. × 3 to 4.5 mm. The chief constituent is a glucoside, *carmic acid* with a characteristic odour.

Sulphuric acid and other reagents precipitate the colouring matter.

It is contained in *Syr. Ferr. Phosph. Co.* and in *Tinct. Cardam. Co.*

OFFICIAL PREPARATION.—*Tinctura Cocci* (*Tinct. Cocc.*), See p. 59.

COCHINEAL (*Coccus*) and also RED SANDAL WOOD (*pterocarpi lignum*), RED Poppy Petals (*rhœados petala*) and SAPPAN (which are not official), are used as colouring agents. Red sandal wood contains a little tannin and is therefore slightly astringent also.

* COCCUS LACCA was known in India from prehistoric days. Fluid lac dye or *alakta* is well-known. It is also used for colouring many medicinal oils by the Kabirajes.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

(1) **AMARANTHUM**, Bordeaux S, Red No. 2, is a dark reddish brown powder prepared synthetically. This in 1% solution is used as a colouring agent unchanged by acids or alkalies, 5 drops colour 1 oz. of water. Bordeaux B in 1% solution is also used.

(2) **CARAMEL**, burnt sugar colouring is a concentrated aqueous solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a dark brown mass is produced : miscible in water in all proportions.

(3) **CROCUS**, Saffron, *kumkuma*, is dark red to pale reddish brown in colour with strong aromatic odour made into syrup (1 in 8) and tincture (1 in 5 of alcohol) and are used as colouring and flavouring agent.

OTHER COLOURING AGENTS (Not official)

ANCHUSA, Alkanet roots have a red colouring matter used for colouring oily or spirituous preparations.

CARMINE, the alum precipitated colouring matter of cochineal is used for colouring dusting powders, ointments and tooth powders : ammoniacal aqueous solution is used for colouring neutral or alkaline mouth washes and mixtures.

NOVAURANTIA, Orange G with **TARTRAZINE 3** and Chloroform water 400 (Liquor Flavus) forms a stable saffron colour unaffected by acids, alkalies or by light : 5 drops of this are sufficient for one ounce of an aqueous fluid.

5. LOCAL IRRITANTS

There are many drugs which when applied to the skin or to the mucous membrane cause irritation characterised by local inflammation and some tissue damage. Several of these in addition, when absorbed are irritant during their excretion through different channels as through the kidneys, also the skin, bronchioles and other places. So, many of these are not suitable for limited and balanced irritant action on the skin only to be of use therapeutically. For local action on the skin, certain volatile oils, (especially oils of turpentine, eucalyptus and cajuput, camphor, menthol, mustard and methyl salicylate), cantharidin and ammonia are often used. Alcohol, chloroform, ether, some preparations of mercury, iodine, mineral acids, alkalies and aconite are also used : these have systemic action also and will be considered separately.

The intensity of the local irritant action of drugs applied externally, may be divided into four stages :

(i) **Rubefacient** : there is redness of the part. The blood vessels dilate, skin feels warm and becomes more sensitive to touch ; if any pain is present, this is relieved and the absorption of any pre-existing inflammatory products is hastened. Later on, often some itching with superficial desquamation follows. *For therapeutic purposes, in largest number of cases, this stage of action should not be exceeded.*

The drugs used as counter-irritant have this type of action.

(ii) **Vesicant** : with more intense irritation, the capillaries widely dilate and become more permeable : fluid exudes from

these blood vessels which collects underneath the cuticle to form at first several small and afterwards, one big blister.

Cantharidin is sometimes applied over a pleural or pericardial effusion or over a painful nerve covering a small area.

(iii) **Pustulant** : if, however, owing to some misadventure, the irritant is either too strong or applied too long especially on the skin glands, there may be some suppuration and formation of pustules.

(iv) **Escharotic** : even more intense action results in destruction of tissues of the area. The agents doing so are called *caustics*. These are (a) strong mineral acids, chromic, laetic, carbolic and trichloroacetic acid : (b) hydroxides of potassium, sodium and calcium : (c) zinc chloride, copper sulphate, silver nitrate and arsenious acid. These have limited use.

Counterirritant *drugs* are now getting out of use. *Radiant Heat* is now largely employed to cause cutaneous or subcutaneous irritation and vaso-dilatation either in the form of poultice, hot air bath or as diathermic treatment.

COUNTER-IRRITANTS

These include agents which by irritating the skin, counter or check certain affections in deeply lying organs.

(i) When a suitable irritant is applied near about an inflamed joint, muscle, nerve or over some pathological fluid as pleural effusion, the action is more or less **direct**. There is a feeling of warmth and slight pain : the superficial blood vessels dilate, the circulation of the place improves and pain if present is relieved : a certain amount of transudation of fluid also takes place in the subcutaneous tissue along with collection of leucocytes. If any infection is present, this is attacked more vigorously. Rubefacient or vesicant action and not as far as pustulation should only be aimed at. Action is probably due to **local axon reflex**, antidromic vaso-dilatation ; stimulation of sensory nerve endings in the skin leads to local reflex vaso-dilatation of the area, the blood vessels concerned being supplied by the same nerve trunk.

Liberation of acetyl choline or a minute quantity of a histamine-like substance from local tissue injury or the existence of a system of nocifensor nerves from the posterior nerve roots (Lewis) have also been thought to be the cause.

(ii) But on the deeper viscera like the stomach and the intestine, the action is different. These are supplied by autonomic nerves which end in different segments of the spinal cord. So severe painful conditions in these viscera are referred to the corresponding spinal segments and therefrom along the sensory and motor nerves coming out of them. The result is that the skin area supplied by these nerves becomes hyperalgesic and the muscles concerned are contracted (*Head's areas*). But this cutaneous localisation is not very accurate and the mechanism

of visceral pain is not yet understood in full detail. Any irritant applied to particular skin areas related in the above way to the painful viscera, relieves the reflex pain by producing a focus of direct pain although of much less intensity and also probably by blocking the visceral reflex path. There are, in addition, some trophic changes in the viscera concerned, improving their blood supply, nutrition and repair and thus helping them in their fight against diseases. This is called **special visceral reflex**.

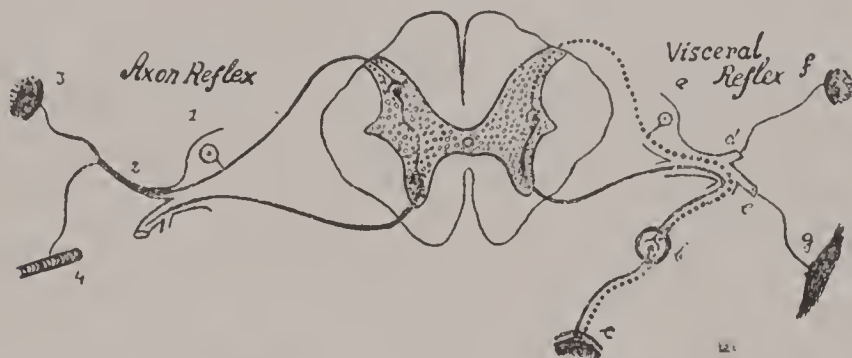


Fig. 4.—*Axon Reflex* : 1. Posterior root ganglion. 2. Sensory nerve root. 3. Sensory nerve termination in the skin. 4. The same in the blood vessel. *Visceral Reflex* : (a) Sympathetic nutrient cell in the posterior root ganglion. (b) Sympathetic ganglion. (c) Visceral termination of the sympathetic. (d) Spinal sensory nerve. (e) Spinal motor nerve. (f) Skin. (g) Muscle.

(iii) There are **constitutional effects** also. With a moderate degree of stimulation the *medullary centres* are activated : the heart-beat and respiration are accelerated and the splanchnic arterics constricted, raising the blood pressure. Metabolism is also altered. Tissue oxidation and nitrogenous elimination are increased, the skin temperature rises and internal temperature falls. Leucocytosis is induced. There are certain general vital effects also : an unconscious or narcotised patient may be roused by sudden skin stimulation.

But if the peripheral irritation is profound, the heart is slowed (through the cardio-inhibitory centre), blood pressure falls (dilatation of the splanchnic vessels) and respiration becomes slow and laboured and a condition of collapse supervenes, best seen in a case of severe burn.

THERAPEUTIC USES.—Counter-irritation is often helpful in a wide variety of cases. It is resorted to (a) for the *relief of pain*, direct in the skin, muscles, joints and nerves or referred from any viscera : in the latter case, the irritant is applied on the corresponding Head's areas ; (b) *absorption* of the exudate of an inflammation ; (c) as a *restorative* in shock as in sudden syncope ; (d) to cause *muscular relaxation* as in convulsion of children or in hysteria also in muscular cramps ; (e) in *internal*

hæmorrhage by causing peripheral vasodilatation and internal anæmia.

The effect should be less than vesication and in no case any further. Counterirritants should be used with care in weak and debilitated persons and in diabetics lest there be extensive tissue sloughing.

The substances used for counterirritation are (a) certain volatile oils, including mustard, (b) cantharidin and (c) ammonia preparations.

A. VOLATILE OILS

These consist of a large group of drugs of variable chemical composition but mostly are *terpenes* (aromatic hydrocarbons) with a general formula of $(C_5H_8)_n$. Some of these, when allowed to stand and also cooled, crystallise and are called *Stearoptenes* : these are Camphor, Menthol and Thymol.

These volatile oils are clear and colourless, rarely bluish or greenish : after prolonged storage, these become yellowish being partially oxidised and made into *Resins*. Some of the resins form emulsion when mixed with water : this is due to their gum-contents and are therefore called *Gum-resins*. *Balsams* are also essential oils mixed with resins and cinnamic or benzoic acid. These different volatile oils and bodies allied to them have more or less similar pharmacological action.

APPLIED EXTERNALLY, or rubbed into the skin, these are irritant and **rubefacient** causing a certain amount of increased vascularity which is followed by slight **anaesthesia** and more powerful of these act as **counterirritant** ; if applied sufficiently long, may cause **vesication**. These are **antiseptic** also by their solubility in lipoids, penetrating into the protoplasm of the bacteria : this is on account of the benzene derivatives to which the terpenes belong, but practical use of this action is limited by their relative insolubility in water.

TAKEN INTERNALLY in a *moderately strong solution*, these give a hot burning taste in the mouth causing salivation : some of these may have a cooling sensation in the beginning. Given in a *diluted form*, by the immediate local action, they dilate the blood vessels of the mouth and other parts of the alimentary canal, increasing the secretion of various digestive ferments, improving appetite. The tone and movement of the stomach are decreased (which probably extends to the sphincters) but that of the intestine generally increased. Flatulence is relieved by eructation and escape of gas from the bowels giving a sense of well-being and comfort. Relief of intestinal distention lessens spasm and if any colicky condition is present, this disappears. The volatile oils augmenting peristalsis expelling gas are therefore **stomachic**, **antispasmodic** and **carminative**.

From local action on the stomach, the heart is stimulated reflexly through the cardioacceleratory centre in the medulla.

The blood vessels of the skin dilate giving a feeling of warmth to the body and a sense of general well-being. But in *bigger doses* especially in *concentrated form*, these cause gastro-intestinal irritation, shown by vomiting and diarrhoea. Oil of turpentine and thymol are **anthelmintics** but as now-a-days better anthelmintics are available, these are not so much used.

Some of these have powerful **odour** which reflexly stimulates the medulla through the olfactory nerves. The agreeable smell of others favours **reflex secretion** of gastric juice even without reaching the stomach.

These increase the number of polymorphonuclear **white corpuscles** : probably these do so by irritating the lymphoid tissues of the alimentary canal.

These have no direct action on the **nervous system** except in poisonous doses when some of these oils cause stimulation of the brain and the medulla, followed by depression. This is probably due to the benzene nucleus in the terpenes. There may be slight necrosis, raising the blood pressure, quickening the respiration and rarely causing convulsion followed by general muscular relaxation from paralysis.

Absorption and Excretion.—These are quickly absorbed from the stomach and intestine and this is in proportion to the volatility. Of the amount absorbed, a part is oxidised and the rest are excreted through the lungs, kidneys and the skin giving their characteristic smell to breath, urine and sweat.

The portion oxidised, mainly as phenols, is excreted in the urine mostly in combination with glycuronic or sulphuric acid.

When these reach the bronchial mucous membrane, these act as **expectorant** (increasing the bronchial secretions). In the same way, they act on the genito-urinary mucous membrane as **diuretic** and **disinfectant**. If, however, the action is very powerful, these may cause renal irritation.

POISONING.—These taken in overdose cause acute irritation of the alimentary tract and also of many viscera especially abdominal, the intensity varying in different oils. Often, vomiting and purging with severe pain in the abdomen and dysuria or anuria follow. The vomit, stool and urine often contain blood and if pregnant, abortion takes place. Collapse follows with feeble pulse and respiration and sometimes convulsion also ending fatally. Some of these oils act on the nervous system : stimulation followed by depression. In the postmortem examination, all the viscera are found markedly congested and blood may collect in the peritoneal cavity.

Some of these again, have generalised action in all parts of the body, but the majority act more on one place than on the other and are classified accordingly.

According to their therapeutic uses, these are classified as follows :

(i) Those specially used as *local irritants*.—Oil of turpentine, colophonium, oil of cade, oil of cajuput, oil of eucalyptus, oil of

rosemary, capsicum and stearoptenes (camphor, menthol and thymol) : effects desired are on the skin, mucous membrane or on the viscera underneath.

(ii) Those for *gastro-intestinal action*.—Purified volatile oil of bitter almond, dill fruit, anise, cardamom, caraway, cloves, cinnamon, coriander, fennel, oil of lavender, lemon peel, oil of peppermint, nutmeg, myrrh and ginger : these are flavouring and carminative.

(iii) Those for *nervous effect* mainly for disagreeable smell.—Valerian and asafetida.

(iv) Those for action on the *bronchial mucous membrane*.—Terebene, terpineol, oil of pine, storax, balsams of Peru and tolu : these are mild expectorants.

(v) Those for *action on the genito-urinary tract*.—Copaiba, oil of sandal wood and buchu. These act as mild antiseptics. But as more dependable antiseptics are now available, as sulphonamides and antibiotics, these are becoming obsolete.

(vi) Those used as *anthelmintic*.—Oil of chenopodium and rarely thymol, very rarely oil of turpentine.

(1) Volatile oils mostly used as Local Irritants.

1. OLEUM TEREBINTHINÆ (*Ol. Terebinth.*), Rectified oil of Turpentine.

The oil is prepared by distilling and rectifying the oleo-resin of various species of *Pinus*, obtained from America, England, France and Russia. These are now being distilled from the *Pinus* of the Himalayan forest also. In Indian Pharmacopœial List, the oleoresin, turpentine, is obtained from *Pinus longifolia* Roxb., *Pinus khasya* Royle and *Pinus excelsa* Wall.

This is a colourless limpid oil with a characteristic smell and bitter pungent taste. It is easily oxidised and so the old oil of turpentine is an ozonising agent. By oxidation, it is converted into oleo-resin. It is a mixture of several terpenes.

It is insoluble in water but soluble at 15.5° in 7 of alcohol (90%) and freely in alcohol (95%), chloroform, solvent ether and in glacial acetic acid. One fl. dr. of mucilage can emulsify $\frac{1}{2}$ fl. dr. of the oil in 1 oz. of water.

DOSE, 3 to 10 minims, 0.5 to 0.6 mil. [Anthelmintic dose, 120 to 240 minims, 8 to 16 ml. is in IND. PHARM. LIST].

OFFICIAL PREPARATIONS.—**Linimentum Terebinthinæ.** See p. 48.

COLOPHONIUM (*Coloph.*), Resin, *Rajan*, IND. PHARM. LIST—Is the residue left after distilling off oil of turpentine from the crude oleo-resin of *Pinus*. Its chief constituent is *abietic acid* : translucent, brittle mass with turpentine smell : the fracture is shining. It is insoluble in water but soluble in alcohol (90%), carbon disulphide and ether.

Emplastrum Colophonii, Adhesive Plaster (1 in 10) Not official. Colophony 10, lead plaster 85 and hard soap 5, prepared at a low temperature.

MASTICHE (Not official) : Mastic is a resinous exudation. Its *solution* in alcohol, solvent ether or chloroform is applied on cotton wool as temporary filling of a carious tooth. A *pigmentum* having mastic 1 oz., castor oil 15 min. and benzene to $2\frac{1}{2}$ fl. oz. is a surgical varnish for wounds.

2. OLEUM EUCALYPTI (*Ol. Eucalypt.*), Oil of eucalyptus.

This is the oil distilled from the fresh leaves of various kinds of *Eucalyptus* and rectified, containing a volatile oil, *eucalyptol*, and a crystallisable resin. It should contain not less than 70% of *cincole*. It grows in Southern India and in the hills of Assam, but is mainly obtained from Australia. It is

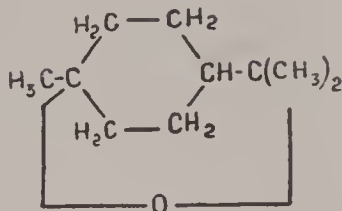
colourless or pale yellow with camporaceous odour and pungent taste, followed by a sensation of cold.

OLEUM EUCALYPTI (*Ind. Pharm. List*), contains not less than 55% w/w of cineole.

DOSE, 1 to 3 minims or 0.06 to 0.2 ml.

INCOMPATIBLES.—Alkalies, iodine, mineral acids and metallic salts.

Eucalyptol (*Eucalyp.*), Cineole, $C_{10}H_{18}O$.—A colourless liquid with a characteristic camphoraceous aromatic odour and pungent cooling taste, prepared from oil of Eucalyptus. It contains not less than 97.5% of w/w cineole. DOSE, 1 to 3 minims or 0.06 to 0.2 ml



3. **OLEUM CAJUPUTI** (*Ol. Cajuput.*) Cajuput oil, *Kaya Putir Tel.*

This is a colourless or yellow oil with camphoraceous odour distilled from the fresh leaves and twigs of various species of *Melaleuca* and rectified by steam distillation: obtained from Singapore and Batavia. Its chief constituent is cineol identical with eucalyptol.

The cineole contents should not be less than 50 or more than 65% w/w.

DOSE, 1 to 3 minims or 0.06 to 0.2 ml.

OFFICIAL PREPARATION.—**Spiritus Cajuputi** (*Sp. Cajuput.*).

DOSE, 5 to 30 minims or 0.3 to 2 ml. See p. 54.

4. **OLEUM CADINUM** (*Ol. Cadin.*), Oil of cade, Juniper tar oil.

This is obtained by the destructive distillation of woody portions of *Juniperus Oxycedrus* that grows in Southern Europe and probably of a composition similar to wood tar.

It is a dark blackish or reddish-brown oily liquid with an aromatic smell and aromatic, bitter, acrid taste: soluble in solvent ether and chloroform but to a less extent in alcohol (90%) and very sparingly in water.

OLEUM CEDRI, Cedar Wood Oil (Not official) obtained by distillation from wood of various species of red cedar is used in microscopy with an oil immersion lens also in perfumery.

5. **CAPSICUM** (*Capsic.*), Capsici Fructus, Pod pepper, *Marich.*

The dried orange-brown or brownish red ripe fruits of *capsicum minimum*: size, 12 to 20 mm. × 7 mm., contain *capsaicin*, a crystallisable acid, a volatile oil, resin, a fatty substance and a volatile alkaloid. Has a characteristic odour and intensely pungent taste.

Made into orange or brownish red powder, **CAPSICI PULVIS** (*Capsic. Pulv.*), Powdered Capsicum.

OFFICIAL PREPARATIONS.—(i) **Tinctura Capsici** (*Tinct. Capsic.*), DOSE, 5 to 15 minims or 0.3 to 1 ml, See p. 59 and (ii) **Unguentum Capsici** (*Ung. Capsic.*). See p. 62.

6. **OLEUM ROSMARINI** (*Ol. Rosmarin.*), Oil of Rosemary.

This is distilled from the flowering plant, *Rosmarinus officinalis*. It is a light yellow or colourless oil obtained from England and Southern Europe. It contains not less than 2% w/w of bornyl acetate and 9% w/w of borneol.

SPIRITUS ROSMARINI (Not official).—Oil of Rosemary 1 and alcohol (90%) 9, (1 in 10). DOSE, 5 to 20 minims orally but more often used as hair lotion.

Pharmacology [and Therapeutics]

This group includes oils of turpentine, eucalyptus, cajuput and rosemary also capsicum and oil of cade. These are mostly used externally as *rubefacient*, *counterirritant* and slightly

analgesic. Oils of turpentine, eucalyptus and cade are *antiseptic* and *deodorant* and the first two are given by inhalation also. Oil of Rosemary has an *agreeable smell*. Internally, oil of eucalyptus and capsicum are *stomachic*, *carminative* and reflex cardiac *stimulant*.

(a) OLEUM TEREBINTHINÆ

APPLIED EXTERNALLY, Oil of Turpentine, more penetrating than most other counter-irritants is **rubefacient** and **counter-irritant**⁶⁻⁷, causing an after sensation of slight *analgesia*. [It is frequently rubbed as liniment on a painful joint, muscle or nerve.] It is fairly readily absorbed from the skin, and much more quickly from the mucous membranes. It is **not** a **very powerful irritant** and does not vesicate unless applied for a long time when a painful slowly healing ulcer is formed.

TAKEN INTERNALLY, it has the usual action of other volatile oils (p. 114), but on account of unpleasant smell, it is not much used orally. It increases the gastro-intestinal movements and secretions and is a **carminative** [but more commonly used in an enema⁸ made up with castor oil and asafœtida. This and turpentine stupe⁹ are frequently prescribed for painful abdominal distension.]

It constricts the **smaller blood vessels** partly by stimulating the medulla and partly by direct local action on the blood vessels: in this way, tends to favour coagulation of blood and act as local **haemostatic** [and so is sometimes given either as inhalation for bleeding from the lungs or by mouth for the same from a gastric ulcer, in $\frac{1}{2}$ to 1 fluid drachm doses well emulsified]. The **blood pressure** slightly rises but with a bigger dose it falls on account of its depressant action on the medulla, heart and the blood vessels.

It is a **deodorant** and also mild **antiseptic** and **expectorant**. It is unsuitable for oral administration [but is sometimes

(6) R

Menthol gr. 5
Camphora gr. 15
Oleum Terebinthinæ
Lin. Sap. aa. m. 120
Oleum Arachis ad. fl. oz. 1

Lin. For chronic irritation.

(7) R

Ol. Terebinth. m. 90
Liq. Ammon. Fort. m. 20
Sp. Ment. Indust. m. 180
Sap. Moll. gr. 200
Aq. Dest. ad. fl. oz. 4

(St. Bart's)

Lin. For chronic inflammation.

(8) R

Ol. Terebinth. m. 60
Ol. Ricin. fl. oz. 1
Tinct. Asafœt. m. 90
Sap. Moll. oz. $1\frac{1}{2}$
Aq. ad. pt. 1

For enema in obstinate constipation.

(9) R

A piece of flannel is dipped into very hot water, wrung out quickly, sprinkled with 8 to 10 drops of oil of turpentine and applied to the abdomen and kept till mild tingling or smarting is produced. This is not to be covered with an impermeable dressing as oil silk, lest the skin be blistered.

given by inhalation¹⁰ with other volatile antiseptics or as steam inhalation, one tea-spoonful of the oil being added to a pint of boiling water in foetid bronchitis, lung abscess and in advanced pulmonary tuberculosis.] It disinfects the upper respiratory passages, diminishes bronchial secretion and relieves congestion. The respiration becomes slightly slower.

It is also an **anthelmintic**¹¹ for tape-worm (given by the mouth) and for thread worms (given per rectum as enema) but is not commonly prescribed for either of these purposes as it is an irritant and is not sufficiently effective.

When absorbed, in the process of excretion it causes **irritation of the kidneys** and slight **diuresis**. Even with a moderate dose, it may cause pain in the loins, scantiness of urine, stranguery and sometimes hæmaturia and should not be prescribed if any renal inflammation is present.

SUMMARY.—Oil of turpentine is a **rubefacient** and **analgesic** of moderate intensity and used in liniments. It is a **carminative** and used as enema or stupes. It is **deodorant**, used as inhalation in lung abscess. It is unsuitable for systemic administration: has a disagreeable smell and causes renal irritation.

Poisoning.—Taken in large doses as $\frac{1}{2}$ fl. oz. for a child and 4 fl. oz. for an adult, it causes fatal poisoning. Abdominal pain, nausea, vomiting, diarrhoea which may be hæmorrhagic, painful micturition, hæmaturia and excitement, delirium, ataxia and coma appear ending finally fatally.

Treatment is stomach wash and demulcents as agar, plantago ovata and egg albumin with water.

(b) OLEUM EUCALYPTI

APPLIED EXTERNALLY, it is less **rubefacient** than other volatile oils and less irritant also but fairly good **analgesic** [and is sometimes used in liniments].

It is a more powerful **antiseptic** than phenol and is slightly **deodorant**. [It is sometimes used as ointment (1 in 50 with soft paraffin) and dissolved in alcohol as a mouth wash. A few drops on the handkerchief, a vapour¹², a spray¹³ or pastilles are used for various inflammatory conditions of the upper respiratory passages both for its antiseptic and deodorant properties].

PASTILLES (Not official) containing menthol 1/20 gr. and eucalyptol $\frac{1}{2}$ min, available in commerce and are often used for sore throat.

(10) R
Menthol gr. 5
Ol. Terebinth.
Ol. Eucalyp.
Creosot.
Sp. Chlorof. aa. min. 120
To inhale in Yeo's inhaler.

(11) R
Ol. Terebinth. min. 120
Mucil. Acac. q.s.
Aq. Ment. Pip. ad. fl. oz. 1
For tape worm, followed by a saline purgative.

(12) R
Ol. Eucalyp.
Tinct. Benzoin. Co. aa. fl. oz. $\frac{1}{2}$
A few drops in boiling water
for inhalation in acute pharyngitis
and tonsillitis.

(13) R
Menthol gr. 3
Camph. gr. 5
Ol. Eucalyp. min. 30
Paraff. Liq. Lev. ad. fl. oz. 1
Spray for chronic nasal and
pharyngeal inflammation.

TAKEN INTERNALLY, in small doses, it is like other volatile oils, a **stomachic**, **carminative** and **reflex cardiac stimulant**. But in bigger doses, is an irritant causing vomiting and diarrhoea with gripes. It is believed to be slightly **antipyretic** and two drops on sugar may be prescribed for common cold. It was sometimes used as **anthelmintic** for ancylostomiasis. During excretion, like other volatile oils, it acts as a mild **diaphoretic**, **expectorant** and **diuretic**. Skin eruptions may appear in persons with idiosyncrasy.

EUCALYPTOL is more frequently prescribed for internal use. It is often preferred for oro-nasal spray because when dried up, it does not leave a varnish-like residue.

(c) OLEUM CAJUPUTI AND CAPSICUM are **rubefacient** and often used EXTERNALLY for **counter-irritation** in various painful conditions. INTERNALLY, the spirit of cajuput and the tincture of capsicum are helpful **sialogogue**, **stomachic** and **carminative**.

(d) OLEUM CADINUM AND COLOPHONIUM

These are used externally only.

OIL OF CADE is an **antiseptic** and is more clean-looking and agreeable than tar which it resembles in action. It also **relieves itching** which makes it especially valuable as ointment in many chronic skin affections¹⁴⁻¹⁵.

RESIN is made into adhesive plaster but now rubber adhesive plasters are more popular. For its **antiseptic** action, it is used as ointment in a chronic ulcer.

(e) OLEUM ROSMARINI

It has an agreeable smell and the usual properties of other volatile oils. It is sometimes mixed with hair oils for its aroma and for promoting the growth of hairs by its **rubefacient** action on the scalp.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

SINAPIS or MUSTARD contains a highly irritant volatile oil. Black mustard contains *sinigrin* (a crystalline glucoside) and an enzyme *myrosin* which with cold water produces allyl isothiocyanate, volatile oil of mustard, responsible for the irritant action. White mustard has *sinalbin* which forms acrinyl isothiocyanate.

Emplastrum Sinapis or mustard plaster is a uniform mixture of powdered black mustard, (deprived of its fixed oil) and a solution of a suitable adhesive, spread usually on paper, each 10 sq. inch of the spread plaster containing 150 grains of powdered mustard. This is applied to the skin for 15 to 20

- (14) R
Ol. Cadin. 10
Sulphur. Sublim. 1
Adeps Lan. Hydros.
Paraff. Moll. Alb. aa. 15
(Ointment for psoriasis.

- (15) R
Oleum Cadinum min. 60
Resorcinol gr. 10
Ichthammol gr. 10
Adeps ad. oz. 1
) Ointment for eczema.

minutes for *counter-irritating* chronic inflammation of many viscera as liver, spleen, stomach, pleuræ, pericardium and also directly over a painful nerve or a muscle. This, kept too long, may cause vesication and as soon as moderate rubefacient effect is produced and the area is slightly smarting, the plaster is removed and a bland oil or vaseline applied. For less powerful action, mustard poultice is preferred.

Taken internally, mustard powder causes irritation of the stomach [and so 2 to 4 tea-spoonfuls of it in a tumbler of warm water is given as drink for causing prompt vomiting in cases of poisoning].

For its *stomachic* properties, mustard flour is often added to various kinds of eatables as condiment and the total expressed oil is largely used for cooking. The total oil of mustard, with cajuput and eucalyptus oils and other rubefacients makes liniments¹⁶.

Oleum Sinapis Volatile is the volatile oil distilled from black mustard seeds without the fixed oil. This has a very pungent and irritant taste, containing not less than 92% of allyl isothiocyanate. This readily penetrates and acts as a powerful irritant.

Linimentum Sinapis.—(3.5%) : Volatile oil of mustard 35, camphor 55, castor oil 125 and alcohol (90%) q.s. to 1000.

PSORALIÆ SEMINA (*Vakuchi, Babchi*) is a reputed medicine of Ayurveda for leucoderma¹⁷, containing an essential oil and a resin. *Linimentum Psoraliæ* is an extract of the oleoresin with olive or arachis oil. This when locally applied, dilates the subcuticular vascular plexuses; the nutrition of the skin improves and melanoblasts are stimulated to form pigment in the decolourized area (Chopra). The oil is sometimes given by percutaneous injection into the affected area by making many punctures.

Non-official Preparations

TINCTURA ARNICÆ FLORUM with water (1 in 8), makes a cooling and soothing lotion¹⁸ for various kinds of bruises.

MUSTARD GAS.—Dichlorethyl sulphide, a synthetic volatile oily fluid is highly irritant to the skin and air passages and causes death. It was used in the second world war.

NITROGEN MUSTARD.—War time experience with mustard gas was that it could produce aplastic anæmia. Researches made it possible to prepare allied compounds to act as systemic cell poison. The compound *di-(2 chloro-ethyl) methylamine hydrochloride* referred to as HN_2 , has been found most satisfactory. It appears to act more quickly than X-rays but effects are less prolonged. It is a temporary palliative agent in Hodgkin's disease, lymphosarcoma, chronic leukæmia, polycythæmia vera, mycosis fungoides, primary lung carcinoma and occasionally in other neoplastic disorders. Thus while X-ray therapy is more useful in localised diseases, nitrogen mustard is particularly useful in severe cases with marked constitutional symptoms and visceral involvement.

DOSE is 0.1 mg./kg. body weight injected into the rubber tubing of a freely flowing saline intravenous infusion, on successive or alternate days for 3 to 6 injections, may be repeated after an interval of not less than 6 to 8 weeks. Vomiting and rigor sometimes follow within a few hours after the injection and rarely leucopenia and thrombocytopenia a few days after.

(16) R

Menthol gr. 5
Camph. gr. 10
Ol. Cajuput. min. 60
Ol. Sinap. ad. fl. oz. 1
A stimulating liniment.

(17) R

Ol. Psoral. Corylifol. min. 60-240
Ol. Oliv. fl. oz. 1

To rub into the area in gradually increasing strength.

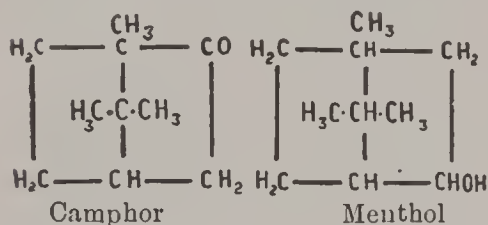
(18) R

Sp. Ment. Indus.
Tinc. Arnica. Fl. aa. min. 50
Aq. Dest. ad. fl. oz. 1
To apply on a bruise.

7. STEAROPTENES, ACTING MAINLY LOCALLY

(1) CAMPHOR (*Camph.*), Camphor, $C_{10}H_{16}O$, *Karpur*.

Camphor is a colourless, transparent crystal or a white crystalline substance obtained from *Cinamomum camphora* which grows in Japan, Formosa and East Indies and is purified by sublimation. It is also prepared synthetically. It should contain not less than 97% of $C_{10}H_{16}O$. Natural Camphor dextro-rotatory and the synthetic isomer is lævo-rotatory.



Solid translucent crystalline masses and powder known as "flowers of camphor". The odour is penetrating and characteristic. The taste is pungent bitter followed by a cool feeling. It volatilises in the usual temperature and burns readily with a smoky flame. Soluble at 15.5° in 700 parts of water, in 1 of alcohol 90%, in 2 of oil of

turpentine, in 0.25 of chloroform and freely soluble in solvent ether and olive oil.

DOSE, 2 to 5 grains or 0.13 to 0.3 gramme.

Camphor is an ingredient of *Injectio Bismuthi Salicylates*, *Linimentum Aconiti*, *Linimentum Belladonnae*, *Linimentum Saponis*, *Linimentum Terebinthinae* and *Unguentum Hydrargyri Compositum*.

Camphor in following admixture undergoes mutual liquefaction.—Camphor and chloral hydrate, camphor and thymol 1 to 1: camphor 2 and beta-naphthol 1: camphor and menthol, camphor and salol 2 to 3 also camphor 4, phenol 12 and water 1.

OFFICIAL PREPARATIONS.—(i) *Aqua Camphoræ* (*Aq. Camph.*), DOSE, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 37. (ii) *Linimentum Camphoræ* (*Lin. Camph.*). This is to be kept in a well-closed container in a cool place. See p. 48. (iii) *Linimentum Camphoræ Ammoniatum* (*Lin. Camph. Ammon.*), Compound Liniment of camphor (1 in 8). See p. 48. (iv) *Spiritus Camphoræ* (*Sp. Camph.*), 1 in 10. DOSE, 5 to 30 minims or 0.3 to 2 ml.: p. 54. (v) *Tinctura Opii Camphorata*, Paregoric, Strength, $\frac{1}{37}$ gr. of morphine in 60 minims or 0.05% ; 1 in 220 of opium. DOSE, 30 to 60 minims or 2 to 4 ml. See p. 59.

OLEUM CAMPHORÆ RECTIFICATUM (*Ol. Camph. Rect.*), Rectified oil or light oil of Camphor (Not official) is the lighter fraction of the oil obtained as a byproduct in the manufacture of Camphor from *Cinnamomum camphora*. It contains not less than 35% w/w of cineole. A colourless or pale yellow liquid with camphoraceous odour and pungent taste. Used as a rubefacient in liniments.

(2) MENTHOL (*Menthol*), Mint Camphor, $C_{10}H_{20}O$.

Menthol is sometimes called peppermint camphor, obtained by cooling the oil distilled from the fresh herb of several varieties of *Menthol* also prepared synthetically (racemic menthol). This is *lævo-menthol* (obtained from volatile oil or synthetically), *racemic menthol* or *mixed* isomeric menthols (any mixture of the stereo-isomers of *p*-menthan-3-ol).

It is in colourless crystalline mass or needle-shaped crystals, giving a sensation of coolness if inhaled or applied locally. It has the smell and taste of peppermint. Obtained from Japan, China and the United States. Almost insoluble in water or glycerin but easily soluble in alcohol (90%), solvent ether, chloroform, essential oils and in light liquid paraffin.

EMPLASTRUM MENTHOL (Not official).—Menthol 15, yellow beeswax 10, resin 75, spread on a piece of calico.

(3) THYMOL (*Thymol*), $C_{10}H_{14}O$, Isopropyl metacresol.

A crystalline phenol obtained from the volatile oils of *Thymus vulgaris*, *Monarda punctata* and *Trachyspermum Ammi*, purified by re-crystallization. It is also prepared synthetically.

Colourless crystals with a pungent aromatic taste. Soluble in water at 15.5°, 1 in 1000, glycerin 1 in 190, olive oil 1 in 2 and freely in alcohol (90%), chloroform and solvent ether.

Dose, $\frac{1}{2}$ to 2 grains or 30 to 120 mg.; 15 to 30 grains or 1 to 2 grammes as an anthelmintic.

Pharmacology [and Therapeutics]

Of the three stearoptenes, CAMPHOR is often used externally as *rubefacient*, *counterirritant* and *analgesic* of moderate intensity. MENTHOL is a more powerful *analgesic*. These and THYMOL are *stomachic* and *carminative*. Camphor is a cerebral and reflex cardiac *stimulant*.

CAMPHOR

The chemical formula is $C_{10}H_{16}O$ and differs from terpenes in having CO (a Ketone link).

APPLIED EXTERNALLY: like other volatile oils, camphor rubbed into the skin, dilates the blood vessels to act as *rubefacient*, and is also slightly *analgesic*. Rectified oil of Camphor is especially useful and may be prescribed as a liniment with an equal part of olive oil or methyl salicylate. Camphor is a mild *antiseptic* and may be used as a *parasiticide*.

TAKEN INTERNALLY, the same rubefacient action is continued. It gives a burning bitter taste to the mouth and causes a sense of warmth in the stomach increasing peristalsis and secretions and is *stomachic* and *carminative*. [It is often used in flatulent diarrhoea¹⁹]. In big doses, it is an irritant and induces nausea and vomiting.

Circulation.—From its local action on the stomach, it reflexly stimulates the heart and the pulse becomes full and bounding. It dilates the blood vessels of the skin and like alcohol, it gives a feeling of warmth. Blood pressure slightly falls. Therefore it acts as a *diaphoretic* and mild *antipyretic* [and is often prescribed for an attack of cold]. Nearly the same action follows a hypodermic injection of it, stimulation of the cutaneous sensory mechanism acting reflexly on the cardiovascular system, increasing the force and rate of heartbeat. [It is frequently used as a diffusible stimulant²⁰ in many conditions of failing heart without organic disease as in a sudden syncope].

Regarding any direct action on the heart, doubts exist. It acts on the heart muscles and the cardiac autonomic centres in a frog but not as constantly in a human being. To a weak and diseased heart, it sometimes gives strength and tends to make the irregular rhythm regular. Some observers also think that

(19) R
Camph. gr. 1
Pulv. Cret. Aromat. c. Opio gr. 20
For summer diarrhoea.

(20) R
Camph.
Alcohol Dehyd. aa. oz. $\frac{1}{2}$
2 to 5 m. on sugar as diffusible
stimulant. (*Rubini's solution*).

it dilates the coronary blood vessels but this is not proved to happen with therapeutic doses. [It was one time given subcutaneously in pneumonia, dissolved in olive oil²¹]. But action is not dependable and is sometimes absent and newer synthetic preparations as leptazol and nikethamide have largely taken up its place. Given in bigger doses, it slows the heart and lowers the blood pressure, due to direct action on the heart muscles and the medullary centres. Like other volatile oils it causes slight leucocytosis.

Respiration.—It has no definite action in therapeutic doses except **slight stimulation** of respiration through the medulla. Like other volatile oils, it is a mild **expectorant**²², gastric irritation reflexly increasing the bronchiolar secretions and used in cough mixtures.

On the Cerebral Cortex, it is decidedly an **excitant** and in some people it acts as an **exhilarant** like alcohol. In small doses, as 5 to 10 grains, it gives a sense of mental comfort and a moderate degree of stimulation. In bigger doses, it causes mental excitement, giddiness, disturbed equilibrium, tremors and finally clonic convulsions. The stimulation later on ends in depression, causing coma, collapse and death. In some cases, not much excitation is found: drowsiness and coma follow more rapidly.

Medullary Centres are also slightly excited causing **quicken- ing of respiration** and temporary **rise of blood pressure**. But bigger doses paralyse them. These paralytic phenomena follow a descending direction, starting from the cerebral centres ending in the medullary, causing death: here it resembles alcohol. Thus excitement, delirium and epileptiform convulsions are followed by paralysis. Death results from respiratory failure.

TREATMENT.—If taken orally recently, the stomach should be washed immediately: the body is kept warm and respiratory stimulants are escribed.

Absorption and Excretion.—It is quickly absorbed from the skin, mucous membrane and the subcutaneous tissues. It is oxidised into camphorol, combines by hepatic activity with glycuronic acid and also with a nitrogenous body and is excreted in the urine as an inert substance. If the liver is inefficient, with 0.5 gm. dose of camphor, no glycuronic acid appears in the urine in 24 hours.

SUMMARY.—Camphor used in liniments is a **rubefacient-analgesic** and mild **antiseptic**. Internally, **stomachic** and **carminative**: **vaso-dilator** and **cardio-accelerator** from gastric reflex and used as **diaphoretic** and **restorative**

(21) R

Camph. gr. 4

Æther. min. 3

Oleum Oli vae min. 15

For hypoder mic injection.

(22) R

Pot. Acet. gr. 15

Tinct. Ipecac. min. 10

Syr. Scill. min. 20

Syr. Tolu. min. 60

Aq. Camph. ad. fl. oz. 1

after syncope : it is a mild **expectorant**. It is readily absorbed, oxidised and excreted in the urine.

Non-official Preparations

CAMPHOR MONOBROMATE, in 2 to 10 grains dose given as cerebral sedative. Insoluble in water and so is made into pill or given in cachet.

CARDATONE.—Sodium compho-sulphonate in 15% solution, 1 to 2 c.c. intramuscularly or intravenously or $1\frac{1}{2}$ to 6 c.c. orally, is cardiac and respiratory stimulant.

SOLUCAMPHRE is 14% solution of *d*-Camphor sulphonate of Diethylene-diamine : given by hypodermic injection which is painless : obtained in 5 c.c. ampoules ; may be given intravenously also 2 to 5 c.c. : orally, solucamphor drops, 50 to 100 drops daily.

MENTHOL

Menthol has an action very much resembling camphor.

Chemically also, it resembles camphor having CO replaced by CHO as in Borneo-camphor but more completely hydrated.

APPLIED EXTERNALLY on the skin, in the form of a stick, called Cone or in 1 in 8 alcoholic solution, it is a powerful **analgesic**. It immediately produces a sensation of cold followed by tingling and numbness. It at first stimulates the sensory nerve fibres carrying the sensation of cold and then penetrates deeper and paralyzes the nerve-endings of ordinary sensation. Further, the skin vessels are dilated and like camphor is a **rubefacient**. [It is frequently prescribed²³⁻²⁴ for various painful conditions especially neuralgias as paints and liniments. It is often applied to the cavity of a painful carious tooth in combination with equal parts of carbolic acid, camphor or chloral hydrate with which it forms an oily liquid. In 2% ointment, it relieves pruritus.

It is a moderately powerful **antiseptic** being more powerful than camphor [and in combination with other volatile oils dissolved in alcohol or liquid paraffin is used as nose and throat spray²⁵]. But being insoluble in water, it is not suitable for general use.

TAKEN INTERNALLY, it is a **gastric sedative** [and is sometimes prescribed in $\frac{1}{4}$ grain doses, for allaying vomiting and hiccough²⁶]. But in bigger doses or if continued long, it is an irritant and tends to upset digestion.

(23) \mathcal{R}
Menthol gr. 10
Lin. Aconit. min. 120
Lin. Bellad.
Lin. Sap. aa. min. 180
Pigmentum. For superficial
painful conditions.

(24) \mathcal{R}
Menthol gr. 5
Camph. gr. 10
Ol. Cinnam. min. 120
Paraff. Moll. Alb. ad. oz. 1
To apply for headache.

(25) \mathcal{R}
Menthol
Chlorbutol aa. gr. 5
Eucalyptol min. 60
Paraff. Liq. Lev. ad. fl. oz. 1
Throat and nose spray.

(26) \mathcal{R}
Menthol gr. $\frac{1}{2}$
Chlorbutol gr. $2\frac{1}{2}$
Ext. Bellad. Sicc. gr. $\frac{1}{4}$
Acacia-Syr. Glucos. q.s.
Pil. one every hour for vomit-
ing and hiccough.

IT IS EXCRETED in the urine as mentho-glycuronic acid : to urine it gives a smell and has a certain amount of **antiseptic** properties.

SUMMARY.—Menthol is used as **analgesic** in liniments, paints and throat sprays along with other drugs of similar action : internally, it is used as **gastric sedative** to control vomiting.

THYMOL

APPLIED EXTERNALLY, Thymol is 25 times more powerful **antiseptic** than phenol and only half as toxic on human being and was one time used in surgery as lotion. A strength of 1 in 1000 is good enough to stop putrefaction but its poor solubility in water is a disadvantage. It is occasionally used with other volatile oils in weak solutions for douching various mucous surfaces²⁷ and in oily or paraffin solution²⁸, sprayed into the nose and throat]. As a mouth wash, it inhibits the growth of *Leptothrix buccalis* associated with tartar formation in the teeth. It is a **deodorant** also. In 10% alcoholic solution it is sometimes applied for ringworm but painful : this is also used in actinomycosis, the sinuses being filled with it.

TAKEN INTERNALLY, in small doses as $\frac{1}{2}$ grain, it is a **carminative** and is sometimes used as an **intestinal antiseptic** and on account of its irritating properties on the mucous membrane of the stomach, it is prescribed as a pill.

One time it was a popular **anthelmintic** for ancylostoma duodenale : after night's light meal, 2 to 3 doses of 30 grains each in cachet or in gelatin capsules were given in the morning every hour followed by a magnesium sulphate purgative, no fatty or alcoholic preparation being administered (these are solvents) till the bowels are thoroughly worked out. The second dose should not be given in a week. Now oil of Chenopodium and Carbon tetrachloride have practically replaced it.

Sometimes it causes **toxic symptoms** such as epigastric pain and by absorption, roaring noise in the ears, impaired hearing, headache, nausea, vomiting, fall of blood pressure and collapse, rarely convulsion. Death follows, from cardiac paralysis.

It is readily absorbed from the intestine ; a greater part of it is broken down in the body and about 25% is excreted, in

- (27) B
 Thymol gr. 2
 Acid Benz. gr. 10
 Acid Boric. gr. 20
 Ol. Eucalyp. min. 30
 Ol. Menth. Pip. min. 20
 Alcohol (90%) ad. fl. oz. 1
 15 drops in 2 oz. of water for gargle.

- (28) B
 Camph.
 Menthol
 Chlorbutol. aa. 2
 Thymol 0.2
 Paraff. Liq. Lev. 100
 To spray into the throat.

the urine in combination with sulphuric and glycuronic acids : it is a renal irritant.

SUMMARY.—Thymol is used as **deodorant-antiseptic** on mucous surfaces in watery or oily solution ; **carminative** and formerly as **anthelmintic** in ancylostoma infection.

Non-official Preparations

"SANITAS" FLUID.—This contains hydrogen peroxide, thymol, soluble camphor and some camphoric acid prepared by the action of water on air oxidised turpentine. A helpful disinfectant.

GLYCO THYMOLINE.—Contains potassium carbonate, sodium benzoate, borax, sodium salicylate, menthol, thymol, glycerin and alcohol, coloured with cochineal. Given internally in 20 to 60 min. doses or as mouth wash in 1 in 8 or 10 dilution.

(ii) Volatile oils used for the Gastro-intestinal action.

1. OLEUM AMYGDALÆ VOLATILE PURIFICATUM (*Ol. Amygdal. Vol. Purif.*), Purified volatile oil of bitter almond.

Prepared from the cake left after pressing out the fixed oil from bitter almonds, peach kernels or apricot kernels, by distillation with water and removal of hydrocyanic acid. It contains not less than 95% benzaldehyde C_7H_6O : a colourless or pale yellow liquid with odour and taste of bitter almonds.

It is an ingredient of *Emulsio Olei Morrhuæ*.

2. ANETHUM (*Aneth.*), Dill fruit, *Misreya*, *Sulpha*, *Sowa*.

The dried ripe fruit of *Anethum graveolens*, 4 mm. \times 2 or 3 mm., cultivated all throughout India and also obtained from Middle and South Europe.

Broadly oval, strongly compressed dorsally and flattened and with a membranous border. Brown in colour and the smell is agreeable and aromatic.

This is made into powder, *ANETHI PULVIS* (*Aneth. Pulv.*).

OFFICIAL PREPARATIONS.—(i) *Oleum Anethi* (*Ol. Aneth.*), Oil of Dill : This is the oil distilled from the fruits, pale yellow in colour having a pungent smell. Contains 43 to 63% w/w of carvone, $C_{10}H_{14}O$. DOSE, 1 to 3 minims or 0.06 to 2 ml. (ii) *Aqua Anethi Concentrata* (*Aq. Aneth. Conc.*), DOSE, 5 to 15 minims or 0.3 to 1 ml. See p. 37.

3. OLEUM ANISI (*Ol. Anis.*), Oil of Anise.

The oil is distilled from the dried, ripe fruit of *Pimpinella Anisum* : colourless or light yellow, with a sweet aromatic taste.

DOSE, 1 to 3 minims or 0.06 to 2 ml.

This is an ingredient of *Elixir Cascaræ Sagradæ* and *Tinctura Opii Camphorata*.

ANISI FRUCTUS, Anise fruit, *Mouri*, (Not official).—The dried ripe fruit of *Pimpinella anisum* obtained from a very large part of India and also from Middle and South Europe : greyish brown, oval fruits covered with short hair, ridged, $\frac{1}{4}$ in. long having an agreeable, aromatic odour.

SPIRITUS ANISI (B.P.C.).—Oil of anise 1 and alcohol (90%) 9. DOSE, 5 to 20 minims or 0.3 to 1.2 ml.

4. CARDAMOMI FRUCTUS (*Cardam. Fruct.*), Cardamom seeds, *Chota Elachi*.

The dried nearly ripe seeds of *Elettaria Cardamomum*, obtained from Malabar and the Western Ghats. The fruit is about 2 cm. long ovoid or oblong : pale buff colour, beaked at the apex and nearly triangular in section. Seeds are many. The odour and taste are strongly aromatic.

Its *volatile oil* contains a terpene, called turpinene.

This is used as an ingredient of *Ext. Colocynth. Co.*, *Pulv. Cret. Aromat.*, *Pulv. Cret. Aromat. c. Opio.*, *Tinct. Gentian. Co.* and *Tinct. Rhei Co.*

Tinctura Cardamomi Composita (*Tinct. Cardam. Co.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 59.

5. CARUM (*Carum*), Caraway fruit, *Sushovi*, *Jira*.

The dried fruits of *Carum carvi*. The fruit is elongated, almost equally 5-sided with ridges and ends tapering, size, 7 mm. x 2 mm., obtained from hills and plains of India. It has an agreeable aromatic odour on account of its *volatile oils*.

This is made into fawn or brown powder, **CARI PULVIS** (*Cari Pulv.*) and used in the preparation of *Tinct. Cardam. Co.*

Oleum Cari (*Ol. Cari*), Oil of Caraway.—It is a colourless oil with its characteristic odour and taste, distilled from the fruits and rectified. It contains *Carvone*, *Carvene* and *Cymene* and carvone contents should be w/w 53 to 63%.

Dose, 1 to 3 minims or 0.06 to 0.2 ml.

6. CARYOPHYLLUM (*Caryoph.*), Cloves, *Labanga*.

This is the dried flowering bud of *Eugenia Caryophyllus*, $\frac{1}{2}$ to $\frac{3}{4}$ in. (10 to 17 mm.) long, reddish brown, subcylindrical and wrinkled calyx tapers downwards and has 4 thick, stiff teeth between which are 4 imbricated petals: has a strong, spicy smell and very pungent aromatic taste. This contains the official *volatile oil*, *caryophyllin* and *gallo-tannic acid* and are usually obtained from Java, Penang and other places.

Powdered Cloves, **CARYOPHYLLI PULVIS** is brown in colour. Used in the preparation of the *Pulv. Cret. Aromat.* and *Pulv. Cret. Aromat. c. Opio.*

Dose, 2 to 5 grains or 0.12 to 0.3 gramme.

OFFICIAL PREPARATIONS.—**Infusum Caryophylli Concentratum** (*Inf. Caryoph. Conc.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 41. (ii) **Infusum Caryophylli** (*Inf. Caryoph.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (iii) **Oleum Caryophylli** (*Ol. Caryoph.*), Oil of Cloves.—A colourless or pale yellow liquid with odour and taste of cloves, distilled from cloves. This becomes reddish brown on exposure to air.

Its chief constituent is *eugenol*, $C_{10}H_{12}O_2$, 85 to 90%, which chemically resembles phenol and a small proportion of *acetyleneugenol* and *caryophyllin*.

Dose, 1 to 3 minims or 0.06 to 0.2 ml.

It is incompatible with mineral acids, lime water, iron salts and gelatin.

Oil of clove is an ingredient of *Pil. Colocynth. et Hyoscy.*

7. CINNAMONUM (*Cinnam.*), Cinnamon bark, *Darchini*.

It is the dried inner bark of the shoots of *cinnamonum zeylanicum*, obtained from the Deccan, Burma, Malaya and Ceylon. Closely rolled quills, about a metre in length and 1 cm. in diameter, containing several smaller quills inside, externally yellowish brown and internally dark brown in colour with a sweet aromatic hot taste.

It contains a *volatile oil*, which is official, also *tannin*, *sugar* and *gum*.

Cinnamon is an ingredient of *Tinct. Catech.*

Powdered Cinnamon, **CINNAMONI PULVIS**, is a dull yellowish brown powder.

This is used for the preparation of *Pulv. Cret. Aromat.*, *Pulv. Cret. Aromat. c. Opio.* and *Tinct. Cardam. Co.*

Oleum Cinnamomi (*Ol. Cinnam.*).—It is an oil distilled from cinnamon bark, yellowish in colour, becoming reddish on keeping. It contains 50 to 65% w/w of *cinnamic aldehyde*, C_9H_8O .

Dose, 1 to 3 minims or 0.06 to 0.2 ml.

Aqua Cinnamomi Concentrata (*Aq. Cinnam. Conc.*), Dose, 5 to 15 minims or 0.3 to 1 ml. See p. 37.

SPIRITUS CINNAMOMI (Not official).—Oil of Cinnamon 1 with alcohol (90%) 9, 1 in 10.

Dose, 5 to 20 minims or 0.3 to 1.2 ml.

8. CORIANDRUM (*Coriand.*), Coriander fruit, *Dhania*.

The dried ripe fruit of *Coriandrum sativum* : almost globular about 3 mm. in diameter, brownish yellow or brown, cultivated all throughout India.

CORIANDRI PULVIS, Powdered Coriander is fawn or brown in colour.

It is an ingredient of *Tinct. Rhei. Co.*

Oleum Coriandri (*Ol. Coriand.*).—A colourless or pale yellow oil distilled from coriander with odour and taste of coriander.

Dose, 1 to 3 minims or 0.06 to 0.2 ml.

Oil of Coriander is an ingredient of *Elixir Casc. Sagr.* and *Ext. Senn. Liq.*

9. FÆNICULUM (*Fænic.*), Fennel fruit (*Madhurica, Bara Mauri*).

The dried ripe fruit of *Fœniculum vulgare* : size, 10 mm. × 4 mm., ovoid oblong, greenish brown or brown in colour with an aromatic odour and slightly sweet taste.

It grows in India, Japan, Central and South Europe.

It resembles anise and its volatile oil is also of the same nature.

Powdered fennel, FÆNICULI PULVIS is a greenish yellow or yellowish brown powder. This is used as an ingredient of *Pulv. Glycyrrh. Co.*

10. LIMONIS CORTEX RECENS (*Limon. Cort. Rec.*), Fresh Lemon Peel.

It is the fresh ripe or nearly ripe outer pericarp of *Citrus Limon*. It contains the volatile oil (which gives the characteristic smell) and a bitter principle.

OFFICIAL PREPARATIONS.—(i) **Oleum Limonis** (*Ol. Limon.*), The oil is obtained by expression from fresh lemon peel, of pale yellow colour with warm slightly bitter taste and smell of lemon. It should contain not less than 4% w/w of aldehydes calculated as citral $C_{10}H_{16}O$. (ii) **Syrupus Limonis** (*Syr. Limon.*), Dose, 30 to 120 minims or 2 to 8 ml. See p. 55. (iii) **Tinctura Limonis** (*Tinct. Limon.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 59.

11. LIMONIS CORTEX SICCATUS (*Limon. Cort. Sicc.*), Dried Lemon Peel.

Dried outer part of the pericarp of ripe or nearly ripe fruit of *Citrus Limon* : has bitter aromatic taste and smell.

It is an ingredient of *Inf. Gent. Co. Conc.*

12. OLEUM LAVANDULÆ (*Ol. Lavand.*), Oil of lavender.

This is an oil distilled from the fresh flowers of *Lavandula officinalis*. Its chief constituents are *Linalol*, an alcohol and *Linalyl acetate*, its ester. It should contain not less than 7% or more than 12% (English oil) or not less than 35% (Foreign oil) in terms of w/w of linalyl acetate.

It is an ingredient of *Linimentum Camphoræ Ammoniatum*.

13. OLEUM MENTHÆ PIPERITÆ (*Ol. Menth. Pip.*), Oil of Peppermint.

This is an oil distilled from the fresh flowering tops of *Mentha piperita*. It contains about 46% of w/w *menthol*, and also *menthone*, a liquid *terpene* and *menthyl acetate* 4 to 9%. It is a colourless or greenish yellow oil, getting thick and reddish on keeping : taste is pungent aromatic which is followed by a sensation of coldness. Soluble at 15.5°, 1 in 4 of alcohol (70%). Obtained from Japan, Britain, United States and other places.

Dose, 1 to 3 minims or 0.06 to 0.2 ml.

It is an ingredient of *Cataplasma. Kaolin.*, *Pil. Rhei. Co.* and *Tab. Sod. Bicarb. Co.*

OFFICIAL PREPARATIONS.—(i) *Aqua Menthæ Piperitæ Concentrata* (*Aq. Menth. Pip. Conc.*), DOSE, 5 to 15 minims or 0·3 to 1 ml. : See p. 37. (ii) *Emulsio Menthæ Piperitæ* (*Emuls. Menth. Pip.*), 1 in 10. DOSE, 5 to 30 minims or 0·3 to 1 ml. : See p. 38. (iii) *Spiritus Menthæ Piperitæ* (*Sp. Menth. Pip.*), 1 in 10. DOSE, 5 to 30 minims or 0·3 to 2 ml. : See p. 54.

14. MYRISTICA (*Myrist.*), Nutmeg, *Jaiphal*.

Dried kernel of the seed of *Myristica fragrans*. Ovoid about 1 in or 20 to 30 mm. long : externally greyish brown with reticulated furrows, internally greyish-red, marbled with brownish red veins. Its chief constituents are a *fixed oil* and a *volatile oil* which is official also amyloextrin.

This is made into fine reddish brown powder, MYRISTICÆ PULVIS.

Nutmeg is used in the preparation of *Pulvis Cretæ Aromaticus* and *Pulvis Cretæ Aromaticus Cum Opio*.

Oleum Myristicæ (*Ol. Myrist.*).—A colourless or pale yellow oil distilled from nutmeg with its characteristic odour and taste.

The oil is an ingredient of *Sp. Ammon. Aromat.* and *Tinct. Valerian. Ammon.*

15. MYRRHA (*Myrrh.*), Myrrh, *Vola*, *Gandharasha*.

This is an oleo-gum-resin containing a volatile oil, *myrrhol*, a gum, a resin, *myrrhin* and a bitter principle.

It is obtained from the stem of *Commiphora molmol* and similar species which grow in Arabia, Somaliland and Western India.

TINCTURA MYRRHÆ (*Tinct. Myrrh.*), DOSE, 30 to 60 minims or 2 to 4 ml. : See p. 59. Myrrh is an ingredient of *Pil. Rhei Co.*

16. ZINGIBER (*Zingib.*), Ginger, *Adraka*.

Ginger is the scraped and dried rhizome of *Zingiber officinale*, grows extensively in India and East and West Indies. Rhizome is flattish, irregularly branched pieces about 7 to 15 cm. × 1·5 to 6·5 cm. with an agreeable odour and pungent taste.

It contains a *volatile oil* which gives the flavour, *gingerol* which gives the pungent taste and some *resins* and allied substances.

Made into light yellow powder, ZINGIBERIS PULVIS (*Zingib. Pulv.*).

DOSE, 5 to 15 grains or 0·3 to 1 gramme.

Powdered Ginger is an ingredient of *Pulv. Rhei. Co.*

OFFICIAL PREPARATIONS.—(i) *Syrupus Zingiberis* (*Syr. Zingib.*), DOSE, 30 to 120 minims or 2 to 8 ml. See p. 55. (ii) *Tinctura Zingiberis Fortis* (*Tinct. Zingib. Fort.*), Essence of ginger. DOSE, 5 to 10 minims or 0·3 to 0·6 ml. See p. 60. (iii) *Tinctura Zingiberis Mitis* (*Tinct. Zingib. Mit.*), DOSE, 30 to 60 minims or 2 to 4 ml. See p. 60.

Pharmacology [and Therapeutics]

This group includes volatile oil of bitter almond, dill fruit, oil of anise, cardamom, caraway, cloves, cinnamon, coriander, fennel, oil of lavender, oil of peppermint, nutmeg, myrrh and ginger. These are mostly used as *sialogogue*, *stomachic* and *carminative*²⁹. Volatile oil of bitter almond, oil of lavender and oil of lemon are used for their *agreeable aroma*.

- (29) R
 Sod. Bicarb. gr. 15
 Sp. Ammon. Aromat.
 Tinct. Cardam. Co.
 Glycer. aa. min. 20
 Aq. Aneth. ad. fl. oz. 1
 Mist. Carminativa B.P.C.

APPLIED EXTERNALLY, oils of clove and cinnamon and ginger are **rubefacient** [and sometimes made into liniments for external application in superficial neuralgias. Oil of peppermint in addition is a powerful **analgesic** also on account of its menthol content : the spirit is added to throat paints for this purpose. This and oils of clove and cinnamon are put into the cavity of a carious tooth for relieving pain.

TAKEN INTERNALLY, these are **sialogogue**, **stomachic** and **carminative** [and so nearly all of these are used in cookery for **flavouring** various food-stuff and are common kitchen requisites. Thus CLOVES, BLACK PEPPER, CINNAMON, CAPSICUM, GINGER, CARDAMOM, ANISE, CORIANDER, CARAWAY, AJOWAN and MUSTARD are found in nearly every house].

Aqueous solutions of the volatile oils of cinnamon, clove, peppermint, anise and dill-fruit are frequently used as **carminative**, often in combination with other carminatives. *Aqua anethi* (Dill water), is the favourite gripe water of babies. Tinctures of ginger and cardamom are good carminatives.

Peppermint, dill, anise, caraway and clove waters are the common make-up of most of the mixtures. Cinnamon in powder is slightly astringent on account of its tannin contents and is frequently added to other antidiarrhœic preparations. The volatile oil of bitter almond is used to disguise the smell of cod-liver oil in emulsion. Oils of nutmeg and lavender are added to pomades and hair oils for their pleasant aroma. Further, oil of nutmeg is a cerebral stimulant and big doses cause epileptiform convulsions.

MYRRH is sometimes used as **stomachic** and **carminative** and is combined with purgative pills. But the tincture is more commonly used in paint³⁰ or in gargle³¹ for spongy gums and in chronic pharyngitis. Like other volatile oils during excretion, it is a mild **diaphoretic**, **expectorant**, **diuretic** and **emmenagogue**.

BETEL and NUTMEG are frequently chewed with areca nut and lime after meals in this country and act as helpful **sialogogue**.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

CINNAMOMUM CASSIA, *Cassia cinnamon* and its preparations *Aqua Cassiæ Concentrata* (oil of cassia 20, alcohol 90% 600 and distilled water to 1000). *Aqua Cassiæ Destillata* (*Cassia cinnamon* 100 g. and water 2000 ml. distilled to 1000 ml.). *Oleum Cassiæ* is the volatile oil distilled with steam from leaves and twigs of *C. Cassiæ*. *Oleum Cinnamomi Foliæ* (distilled from the leaf) : *Spiritus Cassiæ* (oil of cassia 10 and alcohol 95% to 100). DOSES

(30) B

Tinct. Myrrh.
Liq. Iod. Mit. aa. min. 120
Glycer. fl. oz. 1
To paint spongy gums.

(31) B

Tinct. Myrrh. min. 120
Ol. Eucalyp. min. 30
Tinct. Quill. min. 20
Glycerinum ad. oz. 1
 $\frac{1}{2}$ tea-spoonful in 2 oz. of water
for gargle.

and ACTIONS are the same as of the B.P. preparations of *Cinnamomum zelanicum*.

CUMINUM, Cumin (*Jira*) is the ripe fruit of *Cuminum cyminum*; Dose 5 to 10 grs. *Oleum cumini* is the oil distilled from the above containing not less than 16% w/w cuminic aldehyde: Dose, 2 to 4 min. Action is *stomachic* and *carminative*.

OLEUM AJOWAN, Ptychotis oil (*Jowaner tel*) is the oil distilled from *Carum copticum*. This and Aqua Ptychotis are often used as *carminative* for indigestion and flatulence.

OLEUM FÆNICULI, Oil of fennel (*Panmaurir tel*) is the oil distilled from *fœniculum panmorium*. *Aquæ fœniculi concentrata* (from oil dissolved in alcohol) and *destillata* (by distilling fennel with water) are used like other B.P. volatile oil preparations in the same dose as *digestive* and *carminative*.

OLEUM PUDINÆ, Pudina oil distilled from the leaves of *Mentha arvensis* containing 75% of carvone. *Aquæ Pudinx Concentrata* (from oil dissolved in alcohol) and *Pundinx Destillata* (from oil dissolved in water) and *Spiritus Pudinx* (oil in 10 of alcohol 90%) are used internally as *flavouring* *appetizer* and *carminative*.

OLEUM GRAMINIS CITRATI, Lemon grass oil (*Ganda bener tel*) is the oil distilled from *Cymbopogon citratus* containing not less than 70% w/w of aldehydes calculated as *citral*. Used externally as *rubefacient* and in *perfumery*.

AURANTII DULCIS CORTEX contains a volatile oil. *Tincture* and *Syrup* prepared with it are used as *flavouring*.

Non-official Preparations

SODIUM CINNAMATE, (Hetol), Dose, 3 to 5 gr. (soluble in water), was one time used in pulmonary tuberculosis orally or intravenously.

TINCTURA CARMINATIVA, B.P.C.—Essence of ginger 6.25, cardamom 6.85, oils of cinnamon, earaway and clove each 1.04 and alcohol (90%) to 100. Dose, 2 to 10 minims.

SPIRITUS COLONIENSIS B.P.C.—Oils of Bergamot 12.5, Lemon 5, Neroli 2, Rosemary 1.5 and Thyme 0.5 with Concentrated orange flower water 3, Water 41.7 and Alcohol 90% to 1000. *Cologne Spirit*.

Volatile oils used in perfumery.—*Olea Aurantii*, *Bergamottæ*, *Betulæ*, *Citronellæ*, *Geranii*, *Lavandulæ*, *Neroli*, *Rosæ* and *Santali*.

(iii) Volatile oils with disagreeable smell, acting on the Nervous System

VALERIANA (*Valerian.*), Valerian rhizome.

The rhizome of *Valeriana officinalis* is short, dark, yellowish brown in colour, giving off many slender, shrivelled and brittle rootlets, 3 to 4 inches or 7 to 10 cm. long with characteristic disagreeable smell.

This contains a *volatile oil* having valerianic, formic and acetic acids mixed with pinene and borneol. The freshly distilled oil is without smell but when kept exposed to air for some time, it assumes the characteristic penetrating smell.

Powdered Valerian, VALERIANÆ PULVIS (*Valerian. Pulv.*) is light brown or greyish brown in colour.

Tinctura Valerianæ Ammoniata (*Tinct. Valerian. Ammon.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 60.

VALERIANA INDICA *Jatamansi*, (Not official).—This is the dried rhizome and roots of *Valeriana Wallichii* that grows in the Himalayas, from Kumaon to Sikkim.

Dose, 5 to 15 grains or 0.3 to 1 gramme.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

ASAFETIDA (*Asafæct.*): Hing.—An oleo-gum-resin obtained by incising the living rhizome and root of some varieties of *Ferula*. It contains a *volatile oil* with its characteristic unpleasant smell, also resin and gum.

This volatile oil resembles that of garlic, allyl persulphide. It is obtained from Kashmere, Afghanistan, Persia and Turkistan.

Dose, 5 to 15 grains or 0.3 to 1 gramme.

(i) *PILULA ALOES ET ASAFÆTIDÆ* (*Pil. Aloes et Asafæt.*)—Asafetida, aloes, hard soap each 3 and syrup of glucose 1 or q.s.

Dose, 4 to 8 grains or 0.25 to 0.5 gramme.

(ii) *TINCTURA ASAFÆTIDÆ* (*Tinct. Asafæt.*)—Asafetida 2, macerate in alcohol (70%) 10. Resin is precipitated on adding water which is either suspended in mucilage or dissolved in ammonia when dispensed in a mixture.

Dose, 30 to 60 minims or 2 to 4 ml.

Pharmacology [and Therapeutics]

Both Asafetida and Valerian have the usual properties of a volatile oil.

Asafetida is a helpful **carminative** expelling gas and relieving intestinal distention and colic. The tincture is more frequently used in obstinate constipation as an enema mixed with oil of turpentine and castor oil, emulsified with soap (p. 118). It is also applied with castor oil on the abdomen of children to relieve painful distension.

Both asafetida and valerian are, in addition, popular **remedies for hysteria**³²⁻³³. The action is believed to be due to some mental impression caused by the unpleasant odour which is frequently repeated as the patient belches. Esters of valerianic acid contained in the rhizome is now believed, in addition, to have some **sedative effects** also on the central nervous system lessening nervous irritability.

Susruta mentioned this action of the Indian valerian and prescribed it as a cerebral sedative.

Non-official Preparations

ZINCI VALERIANAS.—A white powder, very sparingly soluble in water.

Dose, 1 to 3 grains.

VALIDOL, (Menthyl valerianate), in 10 to 15 minims dose is given as a nerve sedative.

HYSTEROL, (Borneol isovalerianate) is given in 4 grains capsules.

SUMBUL RADIX.—The tincture (Dose, 30 to 60 minims) and the liquid extract (15 to 30 minims) are given in hysteria as nerve sedative.

(iv) Volatile Oils acting mainly on the Bronchial Mucous Membranes

1. TERPINEOL (*Terpineol*), $C_{10}H_{18}O$.

This is a mixture of isomers in which *dl-a*-terpineol predominates, prepared by treating terpene hydrate with a dilute mineral acid and fractioning the crude product by distillation.

(32) B

Ammon. Brom. gr. 10

Tinct. Asafæt. min. 10

Tinct. Valerian Ammon.

Sp. Ammon. Aromat. aa. min. 30

Tinct. Hyosey. min. 40

Aq. ad. fl. oz. 1

One 3 to 4 times daily, for hysteria.

(33) B

Pot. Brom.

Chloral. Hydr. aa. gr. 7½

Ext. Valerian Liq. min. 15

Ext. Glycyrrh. Liq. min. 10

Sp. Aurant. min. 20

Aq. ad. 1 fl. oz.

Bromo-Valerian Elixir for sedation.

A colourless, slightly viscous liquid which may partially solidify : has a pleasant odour and characteristic bitter and slightly pungent taste : insoluble in water, soluble in solvent ether and alcohol.

Terpineol is an ingredient of *Liq. Chloroxylenol*.

TEREBENUM, Terebene, Not official, prepared by agitating oil of turpentine with sulphuric acid and distilling it. It is a colourless or pale yellow liquid with an agreeable odour resembling that of pine wood. It is almost insoluble in water. Dose, 5 to 15 minims or 0.3 to 1 ml.

2. STYRAX PRÆPARATUS (*Styr. Præp.*), Prepared Storax.

This is a viscid brownish yellow balsam with a strong, agreeable smell containing *storesinol* with *cinnamic acid*. It is freely soluble in alcohol (90%) : sparingly in solvent ether. It is obtained from the trunk of *Liquidambar orientalis* which grows in Asia Minor.

This is used in the preparation of *Tinct. Benzoin. Co.*

3. BALSAMUM PERUVIANUM (*Bals. Peruv.*), Balsam of Peru.

This is a blackish liquid balsam, as viscid as treacle, with a pleasant vanillalike odour and burning, slightly bitter taste, containing cinnamic acid, cinnamates, benzoic acid, benzyl benzoate and resin. It contains between 50 to 70% of balsamic ester. It is obtained from the trunk of *Myroxylon Pereiræ* of Central America. Insoluble in water, soluble in 1 of alcohol 90%, soluble in chloroform less so in solvent ether, glacial acetic acid and in light petroleum.

It is emulsified with mucilage of acacia and yolk of egg.

4. BALASMUM TOLUTANUM (*Bals. Tolu.*), Balsam of Tolu.

It is a brownish yellow or brown aromatic tenacious soft semisolid mass which hardens and becomes brittle on keeping. It contains *benzoic acid* and *benzoates* also *benzyl benzoate*, *cinnamic acid* and *cinnamates* with toluene. It contains between 35 to 50% of total balsamic acids. It is obtained from the trunk of *Myroxylon Balsamum* of New Granada. Soluble in alcohol (90%), chloroform, solvent ether and in solutions of fixed alkalis : but not in water.

It is emulsified with mucilage of acacia and yolk of an egg.

Balsam of Tolu is an ingredient of *Tinctura Benzoini Composita*.

OFFICIAL PREPARATIONS.—(i) **Syrupus Tolutanus** (*Syr. Tolu.*), Dose, 30 to 120 minims or 2 to 8 ml. See p. 55. (ii) **Tinctura Tolutana** (*Tinct. Tolu.*), See p. 60. In dispensing it in a mixture, it must be well mixed with mucilage before water is added. Dose, 30 to 60 minims or 2 to 4 ml.

Pharmacology [and Therapeutics]

Volatile oils of this group as terpineol, styrax and balsams of Peru and Tolu have *agreeable aroma* and one time much used for *action on the respiratory system* and now balsam of tolu only is used for this purpose.

TEREBENE^{3 4-3 5} may irritate the kidneys and so should not be given in nephritis. This and Oil of Pine are given by inhalation as **pulmonary antiseptic**.

BALSAM OF TOLU and to some extent, of **PERU** and **OIL OF PINE** are frequently used as **expectorant** and act in the usual

(34) R
Tereben. min. 40
Mag. Carb. Lev. gr. 20
Aq. Dest. ad. fl. oz. 1
A few drops in boiling water
for inhalation.

(35) R
Tereben. min. 10
Mucil. Trag. q.s.
Syr. Tolu. min. 60
Aq. Camph. ad. fl. oz. 1
For chronic bronchitis.

way during excretion like other volatile oils. Syrup of Tolu is a favourite adjunct to cough mixtures³⁶⁻³⁷ but the tincture is better.

STYRAX made into compound tincture of benzoin is also similarly used. It is also made into 1 in 4 ointment and used as **parasiticide**. Balsam of Peru is more commonly used externally for its **antiseptic** and **antiparasitic** action [in scabies, and is best combined with Unguentum Sulphuris in 1 in 8 proportion. It is also used for chronic indolent ulcers and in eczema].

TERPINEOL has a pleasant liliac odour and is used for improving or disguising an undesirable smell either in perfumery or in chloroxylenol solution.

Non-official Preparations

AMMONICUM.—A gum-resin, is sometimes used as an expectorant in chronic bronchitis. Dose, 5 to 15 grains.

GARLIC is a well-known domestic remedy for chronic cough. Its essential oil, Oleum Allii is a powerful antiseptic and Allyl Sulphide, (Dose, $\frac{1}{2}$ to 2 min.) is sometimes prescribed for fœtid bronchitis and pulmonary tuberculosis with cavity. It is also used externally as counter-irritant in many chronic inflammatory conditions.

TERPINE HYDRATE, (2 to 6 grain) and TERPINOL (1 to 2 minims) are made into pills and prescribed in hæmoptysis also in subacute and chronic bronchitis.

OLEUM THYMI, Oil of Thyme., externally is a rubefacient-counter-irritant and internally, a carminative and expectorant (used in bronchitis and whooping cough). Dose, 1 to 5 minims.

PINUS WEBBIANA (*Talispatra*).—This popular Indian medicine is used as expectorant for its volatile oil contents.

SAUSSUREA (*Kushta, Kuth*), the dried root of *Saussurea lappa*, contains an *essential oil* (the active principle), a trace of *glucoside* and an *alkaloid*. It is an *antispasmodic* and *expectorant* in bronchial asthma. It is also a mild *carminative* and *diuretic*. The tincture and extract are given in 30 to 60 min. doses diluted with water. IND. PHARM. LIST.

(v) Volatile oils acting on the Genito-urinary Tract

Several volatile oils were used as **urinary antiseptics** and **diuretics** especially for the treatment of gonorrhœa as copaiba, sandal wood oil, buchu and oil of juniper. These are moderately **expectorant** also. But these have been almost completely replaced by sulphonamides and penicillin which are much more effective and dependable. These are no longer official and are largely of historic interest.

1. COPAIBA (*Copaib.*), Balsam of Copaiba, an oleo-resin is a viscous liquid. Dose, 10 to 30 min. or 0.6 to 2 ml. This prescribed in a mixture, has to be emulsified with $2\frac{1}{2}$ times of mucilage of acacia as it is insoluble in water.

(36) R

Syr. Tolu.

Syr. Scill. aa. min. 30

Inf. Seneg.

Aq. Camph. aa. fl. oz. $\frac{1}{2}$ (Lucus).

For chronic bronchitis.

(37) R

Tinct. Opii Camph.

Syr. Cal. Hypophosph.

Syr. Tolu. aa. min. 20

Linctus. One 3 times daily.

2. **OLEUM SANTALI** (*Ol. Santal.*), Oil of sandal wood, *Chandan Taila*.—This is distilled from the dried heart wood of *Santalum album* that grows in Mysore. DOSE, 5 to 15 minims 0·3 to 1 ml.

3. **BUCHU**, *Buchu Folia*, Buchu leaves. Dried leaves of *Borosma betulina* from Cape of Good Hope.

This is used as *Infusum Buchu Recens* (Fresh Buchu leaves 1, boiling water 2) in DOSE, 1 to 2 fl. oz. or 30 to 60 ml.

4. **OLEUM JUNIPERI**, Oil of Juniper is mainly composed of terpenes and prepared by distilling the full grown unripe fruit of *Juniperus macro-poda*. A colourless or yellow oil with characteristic smell. This is in IND. PHARM. LIST. DOSE, $\frac{1}{2}$ to 3 minims or 0·03 to 0·2 ml.

B. CANTHARIDINUM (*Cantharidin.*), $C_{10}H_{12}O_4$, Not official.

Mylabris or blistering beetle dried (IND. PHARM. LIST) is used as the source of cantharidin. This was one time popular as *counterirritant* and used in the form of *Emplastrum* (0·2% cantharidin) or *Liquor* (0·4% of cantharidin) for many kinds of inflammatory processes, superficial or deep. Thus it was applied on the skin over an inflamed joint or the area of subacute pleurisy threatening effusion, pericarditis, various inflammatory conditions in the abdominal viscera and in superficial neuralgia. The skin should be first cleaned with soap and water and dried. Either the liquor was painted two or three times over a small area of the size of a 4 anna bit or the emplastrum applied for about 4 hours. The blisters formed should be punctured and the fluid evacuated otherwise a little of cantharidin may be absorbed which during excretion, may irritate the kidneys.

For a much less rubefacient effect, it is sometimes combined in minute doses with many hair oils or lotions³⁸ to promote the *growth of hair* where alopecia is due to a deficiency of blood supply to the scalp.

Owing to these irritant properties, it is not used internally. Formerly it was occasionally used as a *diuretic* in minute doses but not safe.

BEE VENOM (Not official).—The isolated venom is suspended in normal saline with 0·5% of phenol and given locally by deep subcutaneous injection in chronic arthritis (available in ampoules) and also rubbed locally in the form of a cream. One such preparation is *Forapin*.

TEAR GASES or *Lacrimators* are used to cause eye irritation to disperse an unruly mob or to force a person to come out from hiding. These are chloracetophenone, brombenzylecyanide, ethyliodoacetate, benzyl iodide and brom-methylethyl ketone.

C. AMMONIUM

1. **LIQUOR AMMONIÆ FORTIS** (*Liq. Ammon. Fort.*), Strong solution of Ammonia.

The gas formed by heating ammonium chloride and slaked lime is dissolved in water making a clear, colourless liquid with strong pungent smell : containing 32·5% w/w of NH_3 .

This is an ingredient of *Liq. Ammon. Acet. Fort.*

OFFICIAL PREPARATIONS.—(i) **Liquor Ammoniaë Dilutus** (*Liq. Ammon. Dil.*) : 10% of NH_3 . See p. 49. (ii) **Linimentum Camphoræ Ammoniatum** (*Lin. Camph. Ammon.*), See p. 48. (iii) **Spiritus Ammoniaë Aromaticus** (*Sp. Ammon. Aromat.*), *Spiritus Ammoniaë Compositus* : Spirit of *Sal volatile*. DOSE, 15 to 60 minims or 1 to 4 ml. See p. 54.

(38) B

Cantharidin gr. 1

Sp. Rosmarin. min. 24

Ol. Ricin. min. 120

Alcohol 90% ad. fl. oz. 6 (Lucus).

A small quantity to be rubbed into the scalp every night and washed in the morning with a weak ammonia solution for alopecia.

2. AMMONII BICARBONAS (*Ammon. Bicarb.*), Ammonium bicarbonate, NH_4HCO_3 .

This is prepared by passing CO_2 through a solution of ammonia. It contains not less than 98% of NH_4HCO_3 .

White crystals or crystalline powder with slight ammoniacal smell and pungent taste. Soluble at 15.5° in $5\frac{1}{2}$ of water, insoluble in alcohol (90%). When ammonium carbonate is ordered, ammonium bicarbonate should be dispensed.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

Ammonium Bicarbonate is an ingredient of *Liq. Ammon. Acet. Fort.* and *Sp. Ammon. Aromat.*

INCOMPATIBLES.—These strong alkalies are incompatible with acids and acid salts, many metallic salts and alkaloids. Strong solution of ammonia is incompatible with iodine, volatile oil and chlorinated lime (explosion).

LIQUOR AMMONII ACETATIS FORTIS and DILUTUS also AMMONII CHLORIDUM have little local but more marked systemic action and have been taken up elsewhere.

AMMONII CARBONAS (Not official), Ammonium carbonate is a variable mixture of NH_4HCO_3 and $\text{NH}_4\text{NH}_2\text{CO}_2$, ammonium hydrogen carbonate and ammonium carbonate.

Pharmacology [and Therapeutics]

The positive-ion Ammonia is very readily absorbed and is as quickly excreted also, mostly as urea in the urine and hence when taken by the mouth, it does not collect in the blood in sufficient concentration to have any specific action. Therefore the main actions of oral administration are dependent upon the negative-ions.

SYSTEMIC ACTION.—If given intravenously in the form of ammonium chloride, 0.15 gm. per kilo body weight, the specific action of the ammonia-ion is best seen. The reflex irritability of the *spinal cord* is markedly increased leading to tetanic convulsions. In addition, the head muscles are affected indicating involvement of the cranial motor system also. In a frog, the motor nerve endings are ultimately paralysed (but not in the mammals) and convulsion is of short duration.

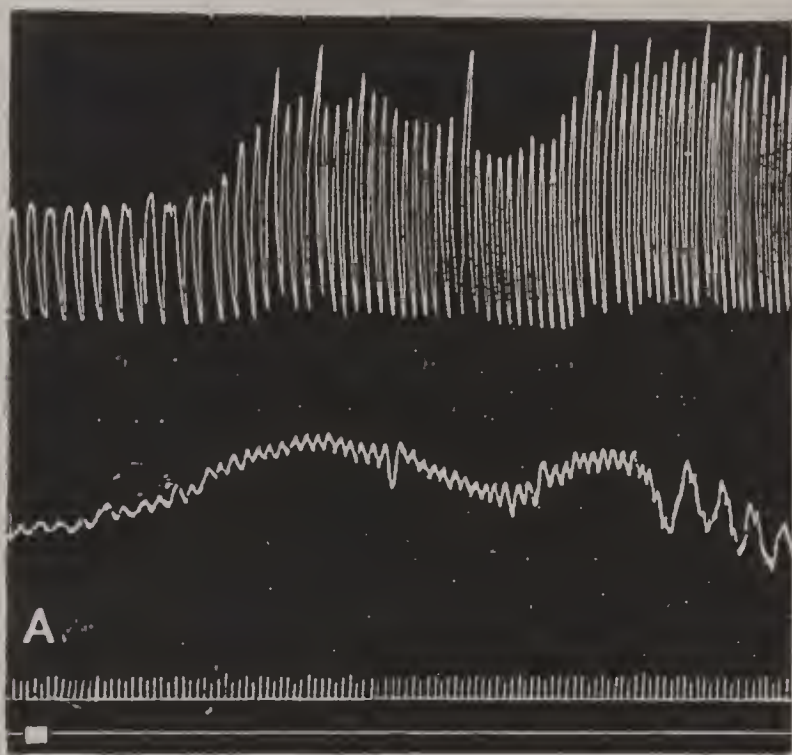
The *medullary centres* are also stimulated. After a temporary stoppage, the respiration becomes quicker and sometimes deeper also. The peripheral arterioles are contracted, the blood pressure rises and the heart beat is slowed from stimulation of the inhibitory centre (though it may sometimes be quickened from direct action on the accelerator mechanism of the heart muscle). Death takes place from respiratory failure but if kept up alive for some time, by artificial respiration recovery is possible as ammonia is rapidly eliminated.

Applied directly on a muscle-nerve preparation of frog, a weak curare-like action (motor nerve paralysis) is produced but this action is absent in mammals.

Liquor Ammonia and Ammonium Bicarbonate

APPLIED ON THE SKIN, owing to its greater diffusibility, liquor ammonia penetrates quicker and deeper but the action

is less sustained. It is therefore much **less corrosive** than the hydrate of fixed alkalies such as sodium or potassium hydrate. Hence it is not much used as a caustic except for milder action, as for neutralising the toxins of bites of insects. In a fairly concentrated form, it is a **vesicant**. In weaker solution, it



(Dixon)

Fig. 5.—Intravenous injection of AM_2CO_3 is given to a cat with vagi cut, at A. Effect is marked stimulation of respiration and rise in blood pressure (Central Vaso-constriction).
Time, in Sec.

is a **rubefacient** and **counterirritant** [and is used in liniments³⁹ and hair lotion⁴⁰].

Both liquor and bicarbonate contain a quantity of volatile ammonia, which when *inhaled*, causes powerful irritation of the nose, resulting in sneezing, coughing and temporary arrest of respiration with immediate closure of the glottis. The trigeminal nerve-endings are directly stimulated and therefrom, **reflexly the medulla**, resulting in excitation of the vasomotor, the cardiac and of the respiratory centres. The arterioles are constricted, blood pressure is raised, the heart is slowed and

- (39) R
Camphor. gr. 10
Liq. Ammon. Fort. min. 120
Acid. Oleic. min. 20
Paraff. Liq. ad. fl. oz. 1
For counter-irritation.

- (40) R
Liq. Ammon. Fort.
Ol. Oliv. aa. min. 60
Sp. Rosmarin. ad. fl. oz. 1
For alopecia areata

the respiration becomes fuller and deeper. [Therefore Ammonium bicarbonate in the form of smelling salts, often scented, is used frequently for syncope⁴¹]. But if very strong or applied too long, it may cause severe inflammation of the nasal mucous membrane.

TAKEN INTERNALLY by the mouth, a similar rubefacient effect is produced. For this purpose, the Bicarbonate is used more frequently and not the Liquor. There is a feeling of warmth in the mouth, throat and the stomach, causing increased vascularity and **secretion of gastric juice**. So it is a **stomachic** and **carminative**. It also causes reflex **stimulation of the heart**, increasing the force and frequency of heart beat. Aromatic spirit of ammonia is frequently used as a stomachic and carminative and as quick restorative in syncope. [It is therefore prescribed in various types of dyspepsia and in conditions associated with feeble cardiac action⁴²].

If concentrated or in a big dose, the bicarbonate causes gastric irritation leading to nausea and **vomiting**. In a dose not sufficient to cause vomiting, this reflexly stimulates the bronchial secretion through the vagal mechanism [and is therefore used as **expectorant** in subacute and chronic bronchitis⁴³. If continued long, this may cause looseness of the bowels. Although alkaloids in general are incompatible with alkalies, codeine salts are not so and may be prescribed with ammonium bicarbonate.

The absorbed ammonia salts are mostly excreted as urea. These enter the portal stream partly as chloride but mostly as carbamate or carbonate of ammonia. In the liver these are changed into urea which during excretion by the kidneys act as **diuretic**. Unlike fixed alkalies, these do not add to the alkali-reserve of the blood: on the contrary do the opposite and by liberating the acid ion, **increase the acidity of the urine** and the blood alkaline reserve is depleted. See ammonium chloride. Ammonium sulphate is a mild purgative.

SUMMARY.—*Externally* ammonia preparations act on account of the presence of volatile ammonia as rubefacient-counterirritant on the skin, as an irritating inhalation on the nasal mucous membrane; from oral administration, as stomachic and carminative (in big doses, emetic) on the stomach and as expectorant, on the bronchial mucous membrane. *The systemic effects* are on the urine causing diuresis (by urea formation) and increasing the urinary acidity.

-
- (41) ℞
 Ol. Lavand. min. 60
 Ammon. Bicarb. oz. 1
 Put up in a stoppered phial.
- (42) ℞
 Camph. gr. 2
 Sp. Ammon. Aromat.
 Sp. Chlorof. aa. min. 20
 Aq. Menth. Pip. ad. fl. oz. 1
 Stimulant mixture.

-
- (43) ℞
 Ammon. Bicarb.
 Pot. Iod. aa. gr. 2
 Tinct. Ipecac.
 Tinct. Scill. aa. min. 10
 Syr. Tolu. min. 60
 Aq. Camph. ad. fl. oz. 1
 For chronic bronchitis.

6. ADSORBENTS

Adsorption is a process of physical fixation of one substance by another without entering into chemical combination. A simple example is decolourization of potassium permanganate solution by filtering through sand. Two drugs are commonly used for adsorbing various toxins. These are, *kaolin* and *charcoal*. Also see p. 6.

KAOLINUM, Kaolin, Bolus Alba

1. KAOLINUM LEVE (*Kaolin. Lev.*), Light Kaolin.

This is purified natural aluminium silicate freed from gritty particles : an inodorous and tasteless, light white powder, insoluble in water and in mineral acids. This is *used orally*.

Dose, $\frac{1}{2}$ to 2 oz. or 15 to 60 grammes.

2. KAOLINUM PONDEROSUM (*Kaolin. Pond.*), Heavy Kaolin.

This is natural aluminum silicate in finely powdered state freed from gritty particles by elutriation. Insoluble in water and dilute acids.

A bland, soft, whitish, non-oxidisable powder used *in pharmacy* for making poultices and pills with all oxidisable substances.

Cataplasma Kaolini (*Cataplasma. Kaolin.*).—(Resembles ANTIPHLOGISTINE). See p. 37. This should be kept in a well-closed container.

Other similar proprietary preparations are *Biphlogistón*, *Antiflamín* and *Numotizine* (this contains in addition guaiacol and creosote).

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY it is a bland powder and is sometimes used as a **protective dressing** to weeping sores. Cataplasma kaolini, applied as a *poultice*, retains the heat fairly long and the hygroscopic action of glycerin withdraws fluid from the diseased area which lessens the inflammation : [applied on many inflammatory conditions superficial or deep and changed every 8 to 12 hours]. Kaolin is not acted on by oxidising or reducing substances as potassium permanganate or silver nitrate. [Used occasionally as a **pill excipient** : but such substances are rarely used internally in pill form].

TAKEN INTERNALLY, light kaolin adsorbs bacterial and metabolic toxins in the stomach and intestine. Light Kaolin is frequently used in gastritis, acute diarrhoea, food poisoning, cholera and in acute bacillary dysentery. It is said to **adsorb** or physically fix up the **bacterial toxin** and prevent its absorption. [One ounce of colloidal kaolin is suspended in 4 to 6 ounces of water and half an ounce of it is given, every half to one hour]. It is a **sedative** to gastro-intestinal mucous membrane and acts by forming a thin protective coating. It is an **antacid** also. [So it is used as aluminium hydroxide gel in gastritis, hyperacidity, gastroduodenal ulcer and colitis]. But if taken for a long time, concretions may form inside the intestine.

Where prolonged administration is necessary, Kaolin is suspended in an emulsion of liquid paraffin⁴⁴ or two tea-spoonfuls of milk of magnesia is administered every morning.

SUMMARY.—The *heavy kaolin* is a poultice and pill basis and *light kaolin* is antacid and gastro-intestinal sedative.

Non-official Preparations

COLLOIDAL KAOLIN is often prescribed orally on account of its fineness : one tea-spoonful is given every hour or less frequently as required.

KEYLENE (Colloidal hydrated silicate of aluminium) has great adsorptive power in bacteria and bacterial toxin. **OSMO KAOLIN** and **COLLOSOL KAOLIN** are other brands of Colloidal Kaolin.

COLLOIDAL ALUMINIUM HYDROXIDE, *Alocol*, is acid adsorbent and astringent. Available as tablets, powder or in emulsion and given after food for flatulence and hyperacidity.

TERRA FULLONICA, **FULLER'S EARTH** (China Clay).—Native hydrated aluminium silicate containing a trace of iron and magnesium : an adsorbent dusting powder, a clarifying and filtering medium also a pill excipient.

UNGUENTUM KAOLINI B.P.C.—Soft paraffin 2 and hard paraffin 1 : melt and add kaolin 1. Mostly used as excipient for making pills of oxidising substances.

DIATOMITE, **TERRA SILICEA PURIFACTA**, *Kieselguhr*.—Mineral remains of a species of algæ : used as adsorbent, dusting powder, filtering medium and pill excipient.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

GELATINUM ALUMINI HYDROXIDI is an aqueous suspension of not less than 3·6% or more than 4·4% of Al_2O_3 in the form of aluminium hydroxide.

This is demulcent and protective to the gastric mucous membrane : in the intestine, it adsorbs metabolic and bacterial toxins without interfering with the digestive enzymes. Available as *Aludrox* and *Kaopal*.

CARBO LIGNI ACTIVATUS (*Carb. Lign. Activat.*), Wood Charcoal, is the residue from destructive distillation of vegetable matter like saw-dust, cellulose residues and cocoa-nut shells treated to increase the adsorptive power. It is a black powder without taste or smell.

Dose, 60 to 240 grains.

Dry freshly heated charcoal has the power of adsorbing oxygen which helps to oxidise organic matter and is occasionally used as *deodorant* and was formerly applied as a poultice over foul sores. In pharmacy, it is used as *decolourising* agent and is used in the filter.

It is also made into a *tooth-powder*, especially when the secretion of the mouth is acid in reaction.

Taken internally, this passes out unchanged and detected in the fæces. The time this takes to pass out of the stomach and finally to appear in the stool often *measures the motor efficiency* of the alimentary canal. It is also sometimes prescribed for *flatulent dyspepsia*⁴⁵ and in *poisoning* by phosphorus and vegetable alkaloids ($\frac{1}{2}$ oz. being given for each grain of the alkaloid), charcoal having the power to adsorb these alkaloids. It is sometimes given in *bacillary dysentery* and *ptomaine poisoning* after preliminary treatment with purgatives to adsorb bacterial toxin and may be combined with Kaolin. Finer the particles of carbon, bigger surface area is presented

- (44) R
Kaolin Lev. gr. 60
Liq. Paraff. min. 120
Pulv. Trag. Co. gr. 15
Sod. Benz. gr. 10
Aq. Chlorof. ad. fl. oz. 1

- (45) R
Beta-naphthol. gr. 1
Carbo. Ligni gr. 10
Ol. Ment. Pip. min. $\frac{1}{2}$
Make tablet : 1 to 4, after food.

and greater is the activity : ULTRA CARBON was a popular proprietary preparation.

CHARKAOLIN and CARBOKEYLENE, Charcoal and Kaolin combined to form granules are given in tea-spoonful doses as adsorbent.

7. ASTRINGENTS

Astringents are drugs that cause **superficial shrinking** of tissues (*L. stringere*, to bind or draw together), also harden them by **coagulating protein**.

Drugs having this action are divided into three groups :

(i) *Inorganic preparations* as calcium hydrate and salts of lead, silver, zinc, copper, iron, aluminium and also to some extent of bismuth : diluted mineral acids.

(ii) Concentrated *alcohols*.

(iii) *Vegetable astringents* containing tannic acid. A large number of vegetable drugs contain tannic acid (see p. 30). Some of these have other powerful active principles also. Of the rest, the main constituent is tannin and these are exclusively used for local action. These are *tannic acid*, *catechu*, *krameria* and *hamamelis* and are described here. Their main use is to lessen *secretion* or to control *bleeding*.

VEGETABLE ASTRINGENTS CONTAINING TANNIC ACID

1. ACIDUM TANNICUM (*Acid. Tann.*), $C_{14}H_{10}O_9$, $2H_2O$, Digallic acid, Tannin.

Galls (various species of *Quercus*) are subjected to a special fermentation and then extracted with water-saturated with ether. (See Galls).

Light brownish or yellowish white powder, light masses or in thin glistening scales, with a characteristic odour and strong astringent taste : acid in reaction. Soluble in 1 of water, alcohol (90%) and in glycerin.

INCOMPATIBLES.—Alkalies, mineral acids ; antimony, lead, silver, ferric salts and salts of many heavy metals ; Alkaloids, gelatin and gum acacia.

OFFICIAL PREPARATIONS.—(i) *Glycerinum Acidi Tannici* (*Glycer. Acid. Tann.*), See p. 41. (ii) *Suppositorium Acidi Tannici* (*Supp. Acid. Tann.*), See p. 54. (iii) *Trochiscus Acidi Tannici* (*Troch. Acid. Tann.*), See p. 61.

2. CATECHU (*Catech.*). *Catechu pallidum*, *Khadir*, *khayer*.

The leaves and young shoots of *Uncaria gambier* are extracted with water and dried,—obtained from Singapore and Eastern Archipelago. Reddish brown cubes, about 25 mm. or in fragments, pale brown internally and soluble in water. Taste is at first bitter and astringent afterwards, sweetish.

Its chief constituent is *Catechu tannic acid*, The others are *catechin*, *quercetin* (colouring) and *gambier-fluorescein*. This is made into pale-brown powder ; CATECHU PULVIS.

OFFICIAL PREPARATION.—*Tinctura Catechu* (*Tinct. Catech.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 59.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

CATECHU NIGRUM (*Catech. Nig.*), Black catechu is the dried extract from the heart wood of *Acacia catechu* : in irregular masses or cube,

dark brown or black in colour, dull or slightly shining masses : very brittle : inodorous, with a bitter astringent taste.

Dose, 5 to 15 grains or 0.3 to 1 gramme.

(i) **PULVIS CATECHU NIGRI COMPOSITUS** (*Pulv. Catech. Nig. Co.*).—Black catechu 50, kino 25, cinnamon 15 and nutmeg 10 (all finely powdered).

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

(ii) **TINCTURA CATECHU NIGRI** (*Tinct. Catech. Nig.*).—Black catechu 200, cinnamon 50 and alcohol (45%) 1000. Macerate.

Dose, 30 to 60 minims or 2 to 4 ml.

3. **KRAMERIA** (*Kramer.*), *Krameria* or *Rhatany* root.

The dried root of *Krameria triandra* (Peruvian rhatany); purplish brown cylindrical pieces with inodorous strongly astringent bark.

Its chief constituents are *Krameria-tannic acid* and *Krameria red*, colouring matter.

This is made into reddish brown powder, **KRAMERIÆ PULVIS**.

OFFICIAL PREPARATIONS.—(i) **Extractum Krameriae Siccum** (*Ext. Kramer. Sicc.*), Dose, 5 to 15 grains or 0.3 to 1 gramme. See p. 39. (ii) **Trochiscus Krameriae** (*Troch. Kramer.*), Lozenge of Rhatany.—1 gr. or 0.06 gramme in each. See p. 61. (iii) **Trochiscus Krameriae et Cocainæ** (*Troch. Kramer. et Cocain.*)—*Krameria* 1 gr. and 1/20 gr. of cocaine hydrochloride in each. See p. 61.

4. **HAMAMELIS** (*Hamam.*), *Witch Hazel* Leaves.

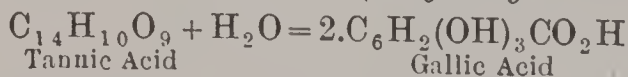
This consists of dried leaves of *Hamamelis virginiana*. The leaves are dark brownish green or green 7 to 15 cm. long, broadly oval to rhomboidal ovate, shortly petiolate : lamina with a sinuate crenate margin and acute apex : asymmetrically cordate at the base : veins pinnate and prominent in the under surface. It contains *Tannic acid*, *Gallic acid*, a bitter principle and a volatile oil.

HAMAMELIDIS PULVIS (*Hamam. Pulv.*) is dull green powdered hamamelis.

OFFICIAL PREPARATIONS.—(i) **Extractum Hamamelidis Liquidum** (*Ext. Hamam. Liq.*), See p. 40. (ii) **Extractum Hamamelidis Siccum** (*Ext. Hamam. Sicc.*), See p. 39. (iii) **Suppositoria Hamamelidis** and (iv) **Suppositoria Hamamelidis et Zinci Oxidi**, See p. 54. (iv) **Unguentum Hamamelidis** (*Ung. Hamam.*), See p. 62.

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All these owe their activities to the presence of tannic acid (the natural tannins are *polyhydroxybenzoic acid*), which is easily decomposed into gallic acid, (*trihydroxybenzoic acid*).



In watery solution, tannic acid undergoes slow hydrolysis and the colour darkens.

APPLIED EXTERNALLY, Tannic acid is a strong astringent and acts best locally on a raw surface and less so on the mucous membranes and even less on the unbroken skin. It readily combines with protein which is coagulated and forms tannate of albumin. It penetrates to some extent and causes a certain amount of drying and hardening of the surface, similar in effect to tanning. If dilute solution is applied on the mucous membrane, a fine layer of mucous and protein forms which protects the cells underneath and lessens sensation.

But a strong solution causes some coagulation of the cell protein and injure the cells. It is sometimes applied to an ulcerated skin and mucous surfaces to reduce secretion⁴⁶⁻⁴⁷. [A 1% solution is used as gargle or vaginal, urethral and rectal lavage : occasionally for throat, nose and rarely for ear and eye conditions. Tinctures of catechu and rhatany or extract of hamamelis, one teaspoonful in 2 ounces of water are also used. A 1 to 4% solution of tannin is sometimes used for local sweating or weeping ulcers. A 5 to 10% tannic acid solution is sprayed on a severe burn : on a less severe burn, tannic acid jelly is a good first aid. The superficial protein being coagulated, a protective coating is formed on which bacteria do not grow. The pain is relieved and absorption of toxin from the wound surface is lessened. Often the healing takes place more or less aseptically, especially in burns of second and third degree. As tannic acid itself is not an antiseptic, an antiseptic like 0.1% solution of acriflavine or of gentian violet is also added. The subsequent sear is usually slight].

Sometimes final healing is slow under dense and firm tan. Further, if tannic acid is applied over a large area, so much may be absorbed into the circulation as to cause focal necrosis of the liver.

Although a dilute solution is protective and slightly lessens the sensibility of the part, a stronger solution, causes coagulation of the tissue cells and acts as an irritant.

By coagulating protein, it plugs the small bleeding vessels and is a haemostatic⁴⁸⁻⁴⁹ although it does not cause any marked vaso-constriction.

These properties are due to both its acid radicle and the tannate base and so a tannin preparation is active in weak acid or neutral albumin-free solution. But when mixed with either an alkali or protein, it becomes inert, alkali tannate or tannin albuminate being formed which has no local action.

TAKEN INTERNALLY, it coagulates superficial protein and shows its astringent action on the *mouth* which feels dry, rough and stiff. The movement of the tongue is somewhat limited with loss of taste. The feeling of constriction is carried down into the throat. [Tannic acid with glycerin forms a favourite application for relaxed throat in chronic pharyngitis : rhatany lozenges are also sometimes prescribed].

(46) R
Acid. Tann.
Acid. Boric. aa. 1
Kaolin. ad. 10
Astringent dusting powder.

47) R
Acid. Tann. gr. 5
Resorcinol gr. 5
Aq. fl. oz. 1
Astringent application.

(48) R
Acid. Tann. gr. 3
Opium Pulv. at. gr. 1
Ol. Theobrom. ad. gr. 15
Suppository for bleeding piles.

(49) R
Acid. Tann.
Tinct. Benzoin. Co. aa. 15
Collod. Flex. 100 (B.P.C.)
To seal a small bleeding point.

In the *stomach*, if food is present it combines with its protein to form tannate of albumin which is not astringent. But as digestion proceeds, tannic acid is liberated. If this is large in quantity or the stomach empty, it combines with protein of gastric mucous membrane and acts as an **irritant** causing nausea, vomiting and diarrhœa. The secretion of pepsin and digestion of protein are not affected in the presence of free hydrochloric acid. Tannic acid may act as a local **hæmostatic**.

It passes down into the *small intestine* and free tannic acid is again liberated by the pancreatic juice. It exerts its astringent action there and also on the upper colon. A fine pellicle of precipitated protein is formed on the intestinal mucous membrane. This **lessens the glandular secretions and peristalsis** and favours the absorption of fluid. Secretion of mucus is also lessened. So the intestinal contents move onwards less rapidly. All these **cause constipation**. [As free tannic acid has a disagreeable taste and irritates the stomach, various preparations of catechu or kino containing a large amount of tannin but liberating this slowly are frequently prescribed either alone or in combination with opium⁵⁰⁻⁵¹ for controlling diarrhœa. The local action on the stomach is also lessened by an insoluble compound like tannalbin or acetyl tannic acid which passes through the stomach unchanged and liberates tannic acid in the small intestine. Extract of hamamelis makes good **pile ointment**].

It **diminishes secretions** of all glands that it reaches directly, probably by precipitating protein.

It **precipitates all alkaloids** and many of the salts of the **heavy metals**. [Often strong tea containing a large amount of tannin is given in poisoning by any of these substances. But the precipitate must be quickly removed either by a stomach wash or brisk purgative, otherwise it may be re-dissolved in the intestine and the poison liberated].

EXCRETION.—A small fraction of tannic acid taken by the mouth is excreted unabsorbed in the stool as gallic acid. The rest is oxidised in the system. Probably it circulates in the blood as alkaline gallates and excreted in the urine in that form. It does not concentrate in the blood in any amount to have astringent action. It cannot be administered intravenously as the coagulated protein forms emboli.

SUMMARY.—The action of tannic acid is limited to the point of application either in the skin or the mucous membrane without systemic action. It is a **local astringent**, coagulating protein and mucus, lessening all glandular secretions, lessening sensibility and sometimes causing shrinking

(50) R
Bism. Carb. gr. 20
Tinct. Catech. min. 30
Aq. Cinnam. fl. oz. 1
One every 3 hours for summer
diarrhœa.

(51) R
Tannalbin gr. 5
Pulv. Cret. Aromt. c.
Opio. gr. 15
Pulv. One every 4 hours for
diarrhœa.

of the superficial epithelium. A dilute solution is of therapeutic value but a very strong solution may cause tissue damage. Tannic acid is a **chemical antidote** in alkaloidal and metallic poisoning.

Non-official Preparations

GALLA.—Nut galls, *Maju fal*. Excrescences on *Quercus infectoria*, due to the puncture and deposit of eggs of *Cynips gallæ tinctorie*. It contains about 60 to 75% of tannic acid and 2 to 5% of gallic acid.

UNGUENTUM GALLÆ CUM OPIO.—Gall 18·5, benzoinated lard or suet 74, powdered opium 7·5 in g. Once a popular ointment for piles.

TANNALBIN, tannate of albumin and **TANNIGEN**, tannylacetate are tasteless, insoluble powders (5 to 15 grains) for diarrhœa.

TANNOFORM, *Methyl ditannin* (compound of formaldehyde and tannin), insoluble powder used as dusting powder or in ointment.

PISTACIA INTEGERRIMA (*Karkota Sringi*).—The galls contain 60% of tannin and a little volatile oil. Used in Ayurvedic and Yunani medicines.

PYROGALLIC ACID (Pyrogallol) is used as 2 to 5% ointment in psoriasis and ringworm and 40% ointment as a caustic for lupus : prepared by heating gallic acid.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

BELÆ FRUCTUS.—The *unripe fruit* of *Ægle Marmelos*, contains tannin, gums, a vegetable acid and a trace of sugar. This is roasted with an outside covering of mud : the softened pulp is made into a drink with water and sugar or with butter milk, and given in subacute dysentery or diarrhœa. A decoction of powdered dried pulp or Liquid extract (**EXTRACTUM BELÆ FRUCTUS LIQUIDUM** prepared by macerating bael 100, chloroform water 1500 and evaporated to 750 ; to this is added alcohol 90%, to make 1000). Dose 60 to 120 minims, is also similarly used. It is a useful domestic remedy.

The ripe fruit is sweet, aromatic and laxative. This with butter milk makes a favourite demulcent drink.

MYROBALAN, *Haritaki*, contains tannic acid, a purgative principle and a vegetable acid. The immature fruit, *Jangi Haritaki*, contains more tannin and is prescribed for diarrhœa : the bowels are cleared of undesirables and diarrhœa checked.

The decoction is used as a gargle for stomatitis : the dried pulp is acid and chewed after meals as a *sialogogue*. For *purgative* action, the outer pulp of 2 to 3 fruits is made into a paste with table salt (which improves the taste) and is given at bed time resulting in one or 2 painless evacuations in the next morning. The liquid extract is also frequently used²². Dose, 60 to 120 minims.

UNGUENTUM MYROBALANI (*Ung. Myrobal.*), 1 in 4 and **UNGUENTUM MYROBALANI CUM OPIO** (with 7·5% of powdered opium) are sometimes used as pile ointment.

KINO.—The juice obtained from incision in the trunk of *Pterocarpus marsipium*, heated and evaporated to dryness. The compound powder containing about 70% of tannin and 5% of opium is sometimes given in diarrhœa²³ in 5 to 20 grains doses. *Tinctura Kino*, Dose 15 to 30 minims is also similarly used.

- (52) \mathcal{R}
 Ext. Myrobalan. Liq. min. 60
 Tinct. Hyoscy. min. 20
 Syr. Zingib. min. 60
 Aq. Aneth. ad. fl. oz. 1
 A mild laxative.

- (53) \mathcal{R}
 Pulv. Ipecac. et Opii.
 Pulv. Kino. Co. aa. gr. 10
 Lactose gr. 15
 Pulv. For diarrhœa.

ANTISEPTICS

8. ANTISEPTICS

Antiseptics (G. *Anti*, against and *septikos*, putrid) are drugs that inhibit the growth of putrefactive organisms as long as they are in contact with them although may not kill them (*bacteriostatic*) and **disinfectants** are drugs that kill these organisms and their spores (*bactericidal*, *germicide*). Many of these are **deodorants** and remove the foul smell as well and many again are both antiseptic and disinfectant also deodorant. So no sharp line can be drawn between them.

There are **PHYSICAL AGENTS** acting as disinfectant as heat (especially moist heat), sun-light, ultra-violet radiation of low wave length, and osmotic difference caused by hypertonic salt or sugar solution.

Apart from these, there is a large group, the **CHEMICAL AGENTS** which act either by killing or enfeebling the pathogenic microbes, inhibiting their growth or by neutralising their toxins.

These activities depend on their penetrability into the protoplasm of the bacteria. This they do either by dissolving or disintegrating the outer fatty envelope. A large number of these are **general protoplasmic poisons**, killing all varieties of living cells almost equally and consequently cannot be applied on bacteria invading the tissues. To be of practical use, the destructive action must be selective, being more powerful on the bacteria than on the tissues of the host.

An **ideal antiseptic** should therefore be non-poisonous to the tissues of the host : further, it should be soluble in water and tissue fluid, moderately penetrating and act fairly quickly. Its chemical stability during storage should be good. It should not be made inert by the putrefactive protein or fat, not corrode metal or fabric nor bleach colour. It should not be absorbed and if absorbed should not cause serious constitutional toxic symptoms. Its price also should be *economical* to be suitable for general use.

Treatment of the wound surface with an antiseptic has many limitations. The infective bacteria may be deeply placed and not reached by the antiseptic applied on the surface. Further, most of the antiseptics in sufficient concentration causes a certain amount of tissue destruction especially with prolonged contact. Antiseptics for internal use may fail to reach a sufficient concentration for an adequate time at the site of the disease with the safe therapeutic doses. Recent introduction of sulphonamides and antibiotics as penicillin and streptomycin and a few other systemic agents, has made a considerable advance and this is going on at such a rapid pace that the use of the chemical antiseptics may soon be a matter of history.

The intensity of the action of a chemical antiseptic depends on the following.

(i) The *nature* and the *number* of *bacteria* present : some are more resistant than others. The spores, if any present, are much more resistant.

The spores of *B. tetani* are not killed in 7 days in acriflavine 1%, ethyl alcohol 70%, lysol 1%, mercury perchloride 0.1% and phenol 5% : but killed in a few hours by hydrogen peroxide 10%, hypochlorous acid 0.25%, iodine in pot. iod. solution 1% and iodine trichloride 1%. Similar variations are seen with other organisms also.

Further, some antiseptics tend to show *specific type of action* : rosaniline basic dyes are very active on Gram-positive organisms but not against Gram-negative ones.

(ii) *Concentration* of the antiseptic as applied on the bacteria : greater the concentration, quicker is the destruction. A low surface tension in solution favours quicker spread. An ideal antiseptic should therefore diffuse readily.

(iii) *Duration* of the period of contact and the *temperature* : the longer the antiseptic is in contact at a higher temperature, the greater is the destructive effect on the bacteria.

(iv) Comparative *solubility* of the antiseptic in the bacterial protoplasm and the solvent used ; it should be at least as soluble in the bacteria as in the solvent : if more soluble in the solvent, the antiseptic action is feeble.

Phenol dissolved in oil or alcohol and mercuric chloride in concentrated alcohol are comparatively inactive on the bacteria.

(v) The presence of *organic substances* : this interferes with the activity of many antiseptics in varying degree ; one that is least affected by *protein* colloids or *lipids* is therapeutically the best.

(vi) A *combination* of antiseptics : this often intensifies the action, but not exactly in mathematical proportion.

The *Triple Dye* is more effective than either of these dyes alone.

(vii) The *tissues* where the antiseptic is required to act : some antiseptics are more suitable for external use than for internal administration and vice versa. Others have special selective power of concentration on one place than on the other, the intensity of action varying accordingly.

Standardisation of Antiseptics

The activity of an antiseptic is determined by culturing different bacteria (usually *E. typhi*) with the antiseptic in several dilutions and noting at what minimum concentration the growth is inhibited in a specified time. This is compared with that of 1% solution of phenol (Rideal-Walker's PHENOL Co-EFFICIENT).

The effect of an antiseptic on bacteria in the living tissue depends on so many variable factors that for practical application, its phenol co-efficient is not too certain a guide.

Tissue toxicity is more difficult to estimate : this may be done by determining the weakest concentration of the compound under examination which inhibits the growth of embryonic tissue (Salle and co-workers, 1935).

The Mode of Action

(i) **SALT ACTION.**—Hypertonic solutions of salt and sugar abstract water from the organisms and inhibit their growth.

(ii) **OXIDATION.**—Some drugs liberate nascent oxygen, as permanganates, hydroxides and halogens which is bactericidal.

Halogens (chlorine and iodine are usually used) act in the presence of water : these combine with hydrogen and liberate oxygen. $2\text{H}_2\text{O} + 2\text{Cl}_2 = 4\text{HCl} + \text{O}_2$.

(iii) **REDUCTION.**—Some liberate hydrogen in contact with water and others abstract oxygen, as formaldehyde, sulphur dioxide and sulphites. $\text{SO}_2 + 2\text{H}_2\text{O} = \text{H}_2\text{SO}_4 + \text{H}_2$.

(iv) **SPECIAL SELECTIVE ACTION.**—Certain substances, either the whole or their particular ions, on dissociation, are protoplasmic poisons and act on different organisms. Coal-tar antiseptics, various synthetic dyes, essential oils, mercury and a large group of acids, alkalies and salts act by their special selective action, in proportion to their degree of dissociation, concentration of H-ions and solubility.

(v) **COAGULATION OF PROTEIN.**—The salts of heavy metals (usually mercury, silver, zinc and copper) and the alcohols combine with the protein of the micro-organisms and kill them. If applied on the surface of an ulcer, these and also tannic acid form a superficial coagulum on which the bacteria cannot thrive for want of nourishment : they consequently die.

Classification of Antiseptics

(i) **SURGICAL ANTISEPTICS** : these are applied to the skin, mucous membranes or to a wound surface in various forms or are used for sterilizing surgeon's hands and surgical appliances. The action is entirely local at the point of contact, though a part of it may be absorbed and cause systemic effects also.

These are (a) *oxidising agents* (hydrogen peroxide, zinc peroxide, potassium chlorate, potassium and other permanganates and chromic acid). (b) *Metallic antiseptics* (especially salts of mercury, copper, silver, aluminium and zinc). (c) *Halogens* (chlorine products, iodine and iodoform). (d) *Tar products* (coal tar, fish tar, wood tar : phenol, cresol, chloroxylenol, trinitrophenol, betanaphthol, resorcinol, acriflavine, proflavine, methylene blue, brilliant green, crystal violet and other dyes : creosote, guaiacol and salicylic acid). (e) *Miscellaneous antiseptics* (Boric acid, borax, formalin, sulphur dioxide and sodium metabisulphite : volatile oils : inorganic acids, acetic acid, benzoic acid, mandelic acid : alcohols :

chrysarobin, dithranol : hydnocarpus oil). (f) *Effective locally as well as by systemic administration* (sulphonamides and antibiotics).

(ii) **INTERNAL ANTISEPTICS** : these are taken internally and act either directly on the alimentary canal (*gastro-intestinal antiseptics*) or during their excretion, either by the lungs (*pulmonary antiseptics*) or by the kidneys (*urinary antiseptics*).

SURGICAL ANTISEPTICS

A. OXIDISING AGENTS

Two groups are included here : (i) those which liberate nascent oxygen as hydrogen peroxide, metallic peroxides, permanganates and sodium perborate and (ii) those which oxidise by other mechanisms as halogens. Molecular oxygen oxidises a fraction of the bacterial protoplasm and kills the bacteria : in general, Gram-positive bacteria, certain spirochaetes and trypanosomes are particularly susceptible. The anaerobic organisms fail to grow in an environment of high oxygen concentration : this has a bacteriostatic effect.

1. **LIQUOR HYDROGENII PEROXIDI** (*Liq. Hydrog. Perox.*), **Liquor hydrogenii dioxidi**.

This is the aqueous solution of Hydrogen Peroxide, prepared by the action of dilute sulphuric acid on barium peroxide in water at a temperature below 10°C. It is a colourless liquid with slightly acid taste : rapidly decomposes in contact with organic matter or alkalis.

It contains 2.5 to 3.5% w/v of H_2O_2 , yielding about 9 to 11 times of its volume of oxygen. This is in IND. PHARM. LIST also.

Pharmacology [and Therapeutics]

The action of hydrogen peroxide is entirely due to its power of liberating oxygen by peroxidase ferments in contact with all tissues. living or dead, and also with various oxidising and reducing substances. The liberated oxygen attacks bacteria and acts as an **antiseptic** and **deodorant**. It does not coagulate albumin and is **non-poisonous**. But the disadvantage is that its action is short-staying and passes off as soon as the liberated oxygen escapes. Its activity is more impaired in contact with an organic matter because oxygen is rapidly liberated and dissipated and the bacteria are left unaffected. For therapeutic purpose, the pharmacopœial 3% solution is usually used. In stronger solution. it irritates the sores, precipitates protein and causes a certain amount of pain.

It is a moderately powerful **hæmostatic** and is sometimes used for stopping bleeding from the nose.

It destroys pus and **disintegrates necrosed tissues** [and is often used in cleansing of a septic wound by removing sloughs superficial or deep also for painlessly releasing an adherent dressing].

It is a useful gargle for septic throat⁵⁴ especially in Vincent's stomatitis : undiluted official solution may be used as gargle 3 to 4 times daily. It is also applied to a fresh wound, contaminated with street dust, to destroy tetanus bacilli which may be present, these being susceptible to oxygen.

INTERNALLY, it is seldom used for antiseptic action. Given subcutaneously, a large amount of oxygen is liberated and some of it escapes into the blood. This if sufficiently large, may cause gas embolism and death.

One of the commercial product is called *Peroxyl*.

SUMMARY.—Hydrogen peroxide is an **oxidising antiseptic** mostly used to disintegrate sloughs and remove adherent dressings from septic wounds. It is non-irritating and nontoxic but the action short-staying.

2. ZINCI PEROXIDUM (*Zinc. Peroxid.*). ZnO_2 .

Medicinal Zinc Peroxide is a mixture of zinc peroxide, zinc oxide and zinc hydroxide, obtained by the action of hydrogen peroxide on zinc oxide. This contains not less than 75% of ZnO_2 .

A fine inodorous white or faintly yellow powder, almost insoluble in water, soluble in dilute mineral acids.

Zinc peroxide slowly liberates nascent oxygen leaving a residue of zinc oxide. This is therefore an oxidising **antiseptic** and mildly **astringent**. It is used as dusting powder in sloughing wounds. It is of value in mouth infection from anaerobic micro-organisms, prescribed 1 in 4 suspension. A 40% suspension is of use for wound infection.

Non-official Preparations

(i) SODIUM PERBORATE, ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$), releases nascent oxygen in the presence of water and is mainly used for the treatment of oral sepsis as mouth wash (2% solution) and added to dentrifices.

(ii) MAGNESII PEROXIDUM, Magnesium Perhydrol, MgO_2 ,⁵⁵.

Dose, 15 to 60 grs. It is more stable than hydrogen peroxide. It makes good tooth powder with creta : it is useful orally in gastrointestinal fermentation.

(iii) SODIUM PEROXIDE is a white water-soluble powder and readily releases oxygen leaving strongly basic sodium oxide. It is sometimes used for the removal of acne and comedones.

3. POTASSII CHLORAS (*Pot. Chloras*), KClO_3 .

Prepared by electrolysis of a hot solution of potassium chloride, contains not less than 99% of KCl_3 . Colourless crystals or white powder with a cool saline taste. Soluble at 15.5° , in 16 of water, in 30 of glycerin and insoluble in alcohol (90%).

Dose, 6 to 10 grains or 0.3 to 0.6 gramme.

TABELLÆ POTASSII CHLORATIS (*Tab. Pot. Chlorat.*) is prepared by dry granulation and compression. Each tablet, if not otherwise stated, contains 5 grains.

Dose as of Pot. Chloras.

(54) R
Liq. Hydrog. Perox. 500
Ol. Ment. Pip. 1
Saccharin. Solub. 3
Aq. Thymol. 470 (Martindale).
Antiseptic mouth wash.

(55) R
Mag. Perhydrol.
Creta.
Sod. Bicarb. aa. gr. 15
Pulv. For acidity after food.

TROCHISCUS POTASSII CHLORATIS (Not official).—Dose, 1 to 6 lozenges of 3 grs. each, made with rose basis.

INCOMPATIBLES.—It readily explodes when rubbed with easily oxidisable substances as charcoal, glycerin, sugar, sulphur and tannin.

It is incompatible with ferrous salts, iodides, nitrites, hypophosphites, mineral acids and calomel.

Pharmacology [and Therapeutics]

Although otherwise fairly stable, Potassium chlorate is believed to be decomposed in contact with septic tissues, liberating nascent oxygen which has a certain amount of **local antiseptic** action. But recent observations tend to show that no oxygen is liberated at the body temperature and its beneficial effects are mainly due to local *salt action*. [Tablets⁵⁶ and lozenges are sometimes sucked in stomatitis and septic condition of the throat and is used as gargle⁵⁷ also].

TAKEN INTERNALLY, it has a saline taste and in concentrated solution, causes **nausea and vomiting** from local salt action on the stomach : when absorbed it is mostly excreted unchanged in the urine causing **diuresis** from similar action on the kidneys.

If given in a moderate dose as 10 to 15 grains, 3 or 4 times daily, the salt is readily absorbed into the blood and a little of it is eliminated by the salivary, sweat and mammary glands, and various mucous membranes. If any septic condition existed in these places, it was hoped that it might exert a moderate degree of **antiseptic** action liberating nascent oxygen. [It is sometimes prescribed for stomatitis, septic tonsillitis and pharyngitis⁵⁸ and occasionally for cystitis]. But probably it has no such action.

In certain cases, **toxic symptoms** appear either from a single big dose or as cumulative effect of prolonged administration. These are pain in the epigastrium and severe vomiting followed by diarrhoea also diminution or suppression of urine. The skin and the mucous membrane are cyanosed. The pulse and respiration become feeble and death follows from profound depression. It is believed that hæmoglobin of the blood is changed into **methæmoglobin** and afterwards into **hæmatin**. If taken in small doses this change is not much and the pigment liberated is partly transformed into bile and partly excreted by the kidneys. But with a larger dose, so many red blood

- | | |
|---|---------------------------------|
| (56) R | Aq. Dest. fl. oz. 2 |
| Pot. Chloras. gr. 2 | Paint or gargle in 1 in 10 sol. |
| Acid. Benz. gr. 1 | For ulcerative stomatitis. |
| Menthol gr. $\frac{1}{2}$ | (58) R |
| Borax gr. 2 | Pot. Chloras. gr. 10 |
| Oleum Rosæ min. $\frac{1}{2}$: tablet. | Liq. Ferr. Perchlor. min. 15 |
| For septic throat. | Glycerinum min. 20 |
| (57) R | Aq. Chlorof. ad. fl. oz. 1 |
| Pot. Chloras. gr. 60 | For acute tonsillitis. |
| Phenol gr. 30 | |

corpuscles are broken down that the liver, and much more so the kidneys, are clogged with the cellular debris and blood pigment. The bile is thickened and there is jaundice. The urine is scanty, dark brown in colour and loaded with albumin, casts and disintegrated red blood corpuscles : it contains chlorates also. Oxygenation of blood is interfered with resulting in asphyxia. Ultimately, the urinary secretion is markedly reduced and may be totally suppressed causing uræmia.

The above explanations of its toxic action have recently been questioned. (i) It is a stable salt and has practically no oxidizing action at body temperature, and (ii) in animals showing symptoms of acute or sub-acute poisoning, methæmoglobin is present only in a small percentage of cases. (Cushny).

SUMMARY.—Potassium chlorate is used as gargle, in 2 to 4% solution also as tablets to suck in stomatitis : probably acts by salt action. It is of no dependable value by oral administration : may cause toxic symptoms.

4. POTASSII PERMANGANAS (*Pot. Permang.*), KMnO_4 .

Prepared by the action of CO_2 on an aqueous solution of potassium manganate. It contains not less than 92% of KMnO_4 . Dark purple, slender, prismatic crystals with a metallic lustre and sweet astringent taste : soluble 1 in 20 of water. It readily loses its oxygen when in contact with organic matter.

DOSE, 1 to 3 grains or 60 to 200 mg.

INCOMPATIBLES.—All vegetable oxidisable matter, ammonia, ammonia salts and alkaloids.

Pharmacology [and Therapeutics]

Although Manganese is often found in the blood and tissues, its function is unknown. No systemic effect is produced when it is given by the mouth. But if injected subcutaneously or intravenously, like other heavy metals it causes convulsions and gastro-intestinal irritation. In minute doses, probably, it temporarily increases the *antitoxic* power of the blood and is sometimes given hypodermically in boils, abscesses and carbuncles. It has also probably some *hæmatinic action* as an adjunct to iron and copper.

Potassium Permanganate is mostly used externally as a powerful **oxidising agent** of all organic matters. As oxygen is easily evolved and dissipated, its action is very short-staying and it soon becomes inert.

APPLIED TO THE SKIN, especially in a concentrated (5%) solution, it causes a brownish discolouration and kills the superficial tissues causing a shallow ulcer. Such a solution on the mucous membranes is **caustic**. In a much weaker solution, it is **astringent, antiseptic and deodorant**.

[It is applied in the form of crystals, to the wound of a bite by animals especially snake-bite : the site is scarified previously so that the medicine may have free access : the venom is.

oxidised and destroyed. In 1 to 2% solution, it is applied on various foul sores and ulcers as *cancrum oris*. In 1 in 2000 or better commenced in more diluted solution, it is used for douching various mucous surfaces as in gonorrhœa, chronic bacillary dysentery, ozœna and in stomatitis. For this purpose, sometimes Sodium, Calcium or Zinc permanganate (the last not stronger than 1 in 4000 solution) also is used. Potassium permanganate is sometimes used for disinfecting drains and wells. Sufficient permanganate should be used to leave a faint trace of pink colour].

Permanganate solution stains linen which stain is easily removed by washing with weak sulphurous acid solution.

INTERNALLY, in the alimentary canal, permanganates oxidise organic matters and act as a **disinfectant**. But the action is less dependable. [It was used by Rogers in Cholera. Two grains pills are prepared with kaolin and vaseline and coated with sandarac varnish or keratin, 2 pills given every $\frac{1}{2}$ hour till the stool changed colour. This treatment is now-a-days nearly obsolete].

One grain of it in 1 pint of warm distilled water is frequently used as a stomach wash in **alkaloidal** and **phosphorus poisoning** also in certain barbiturates and chloral hydrate poisoning. The poison is oxidised and made innocuous.

Alkaloids resistant to permanganate oxidation are atropine and cocaine.

This is occasionally given per rectum in lobar pneumonia, high blood pressure and in certain chronic disorders of metabolism and believed to be of some value.

Non-official Preparations

CALCIUM PERMANGANATE, in $\frac{1}{4}$ gr. pills or 1 in 2000 solution as a drink was formerly frequently given in cholera. It is used externally and is probably more powerful than the potassium salt.

SODIUM PERMANGANATE, is also used for permanganate action. CONDY'S RED FLUID a proprietary preparation, contains sulphate and permanganate of sodium (2%) is frequently used adequately diluted.

ZINC PERMANGANATE is an astringent oxidising agent used in gonorrhœa, pyorrhœa alveolaris and in inflammatory conditions of other mucous membranes in 1 in 5000 solution.

MANGANESE BUTYRATE one or 1.5 c.c. of 1% solution were given intramuscularly twice a week for local septic processes as boils, carbuncles, erysipelas or whitlow of strepto or staphylococcal origin.

5. CHROMII TRIOXIDUM (*Chrom. Triox.*), Chromic acid CrO_3 .

Crimson acicular crystals or dark brown masses, inodorous, corrosive and deliquescent : prepared by the action of sulphuric acid on potassium bicarbonate : very soluble in water and in solvent ether.

It readily parts with oxygen and explodes with glycerin or alcohol (90%), ether and certain organic substances.

LIQUOR ACIDI CHROMICI, (Not official) is used externally : Chromic acid 25 and distilled water 100. (25% solution).

INCOMPATIBLES.—All oxidisable substances with which it forms explosive compounds.

Pharmacology [and Therapeutics]

A solution of Chromic acid, on account of its positive ion chromium is a very powerful **caustic**. It is also an **oxidising agent** and **deodorant**. [It is sometimes used in 25% solution to destroy warts and condylomata: in 10% solution for rodent ulcer and 5% solution for foul sores especially *cancrum oris*. A weak solution, as 1% or less, has been used in chronic inflammatory conditions of various mucous surfaces as stomatitis, colitis, chronic gonorrhœa and leucorrhœa⁵⁹].

CHROMIC ACID POISONING is sometimes seen in electrotyping, dyeing and plating industries. Irritating effects appear on the skin (causing deep burrows in the fingers) and the upper respiratory passages (inflammation, ulceration and finally perforation of the nasal septum). If absorbed in sufficient quantity, there may be nephritis.

B. HALOGEN GROUP

(Chlorine, Bromine and Iodine)

CHLORINE

1. CALX CHLORINATA (*Calx. Chlorinat.*), Bleaching powder, Chlorinated lime, $\text{CaCl}_2\text{O}_2 \cdot \text{CaCl}_2$.

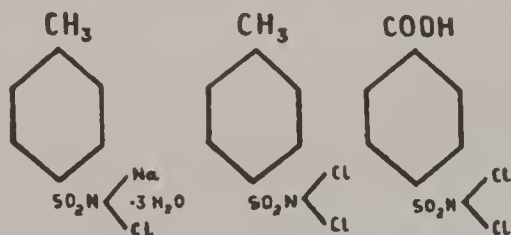
Prepared by placing slaked lime (calcium hydroxide) into chlorine gas, till it absorbs not less than 30% w/w of available chlorine. **IND. PHARM. LIST** requires not less than 25% w/w of available chlorine. A dull white powder, smelling of chlorine, gradually decomposes on exposure to air.

OFFICIAL PREPARATION.—*Liquor Sodæ Chlorinatæ Chirurgicæ* (*Dakin's solution*), See p. 50. It is stocked in cold, in a coloured stoppered bottle. The strength of chlorine gradually deteriorates.

2. CHLORAMINA (*Chloram.*), Chloramine-T,



This is sodium *p*-toluenesulphonchloroamide. Prepared by the action of sodium hypochlorite solution on *p*-toluene sulphonamide. White



Chloramine-T Dichloramine-T Halazone

crystals or crystalline powder with chlorine smell and bitter unpleasant taste. Soluble in 7 parts of water at 15.5° and in 2 parts of boiling water. To be stored in a cool dark place.

(59) B

Chrom. Triox. gr. 10

Aq. Dest. fl. oz. 1

Mild caustic for mucous surface.

Pharmacology [and Therapeutics]

Chlorine in various forms is used as an **antiseptic**, **disinfectant** and **deodorant** for many septic conditions. But in a strong solution, it is very **irritant** and even **vesicant**.

It acts mainly by virtue of its affinity for water, forming hydrochloric acid and liberating nascent oxygen, also partly by chlorination of the organic matter, hypochlorite solution being a powerful solvent for necrotic tissues. Chlorine reacts with the hydrogen of the amino groups to form chloroamines which is a powerful antiseptic. Concentration of chlorine necessary to *kill* most organisms in 15 to 30 seconds varies between 0.1 to 0.25 parts per million. Phenol coefficient of element chlorine for different bacteria varies between 150 and 300. Chlorine is also **viricidal** and **amœbicidal**. But tubercle bacilli are comparatively resistant. The gas itself is so irritant that even 1 in. 100,000 of it in the air causes painful irritation of the eyes and upper respiratory passages.

[The gas is sometimes used for fumigating the sick room. But an effective concentration bleaches colours and corrodes clothes. Chlorinated lime is too irritant to be used on tissues and is more frequently used for disinfecting drains, urinals, and privies and is a helpful deodorant : 4 ounces of it in one gallon of water is sufficient].

Hypochlorous acid gas and *hypochlorites* in air disinfection of a room are moderately affective with relative humidity of 70 to 90% : may corrode metals. *Propylene* and *triethylene glycols* at a concentration of 0.069 mg. and 0.0044 mg. per litre are more effective, are nontoxic and noncorrosive.

[Chlorine is also used as gargle in oral sepsis but elemental chlorine is difficult to handle. Hypochlorites in dilute solution, as Dakin's solution, are used for dressing septic wounds or irrigating cavities⁶⁰. There are other suitable hypochlorite preparations also, one sometimes used is Eusol⁶¹ lotion or Eupad⁶² powder].

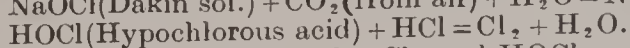
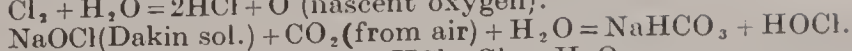
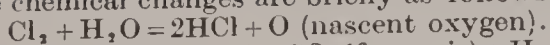
The hypochlorites in watery solution liberate chlorine rapidly in the presence of protein. Applied to a septic wound, although the disinfecting action is rapid, the **effect is short-staying** and not sustained, chlorine being fixed by protein. Further, these act as strongly on the tissue proteins as on the septic organisms which is a disadvantage.

- (60) B
 "Milton" Disinfectant.
 1 in 50 or more for irrigation.
 (Contains 1% sodium hypochlorite in soluble form).
 (61) B
 Bleaching powder 12½ gm.
 Potable Water 1 litre.
 Mix and add Boric acid 12½ gm.

Allow it to stand for 3 hours and filter : has 0.27% HOCl and used fresh.

- (62) B
 Mix Bleaching powder and Boric acid in equal parts.
 Used as dry dressing between two layers of gauze.

The chemical changes are briefly as follows :



As the action is reversible, O_2 , Cl_2 and HOCl are successively formed.

An *acid medium* having pH nearing 6.0 and slightly *higher temperature* increase the germicidal effect.

In *water disinfection*, the amount of chlorine necessary depends on the amount of extraneous matter present in the water. A residual chlorine content of 0.2 to 0.4 parts per million of water presents a satisfactory margin of safety. In a relatively pure water 0.5 parts of chlorine per million is sufficient but a grossly polluted water may require 20 parts or more per million.

Formerly a weak solution of chlorine, prepared by the action of strong hydrochloric acid on potassium chlorate was given internally as an **intestinal antiseptic** especially in typhoid fever. But it is irritant, effects are uncertain and is not now-a-days prescribed.

Chloramine-T contains 12.6% of chlorine, is more stable and has more sustained action and is used for **washing foul sores** in 1 to 2% watery solution or as an ointment⁶³. One half to 1% or a still weaker solution is useful as gargle or as nasal, urethral or vaginal wash. It is more powerful in protein-free medium : 1 in 250,000 solution of it with a little citric acid in water kills the organism of bowel diseases and is **water-disinfectant**. Even in the presence of protein, it liberates chlorine more slowly, is more *stable, neutral* in reaction, *less irritating* than hypochlorite solution and with *four times the bactericidal* power. It has however less solvent action on necrotic tissues.

SUMMARY.—Chlorinated lime is mainly used for **disinfection** of drains, privies and urinals : Dakin's solution, for septic wounds and chloramine, for water disinfection.

Non-official Preparations

CHLORCOSANE, Chlorinated Paraffin, light yellow bland oil for naso-pharyngeal spray.

DI-CHLORAMINE-T (about 30% chlorine) is insoluble in water, soluble in oil and acts slowly : 2% ointment is made with Chlorinated Eucalyptol-paraffin. Applied to the naso-pharynx as spray⁶⁴ for sub-acute or chronic processes.

HALAZONE, is used to disinfect water, a 15 mg. tablet being required for one litre.

SUCCINCHLORIMIDE, 11.6 mg. can disinfect one litre of water in 20 minutes.

(63) B

Chloramine-T 10

Sod. Stearas. 86

Aq. Steril. 4

Ung. For a granulating wound.

(64) B

Dichloramine-T 8

Chlorcosane 92

Mix. For throat spray.

BROMUM (Not official)

Bromine in the free state is hardly used for therapeutic purpose.

It has the same action as chlorine and is highly **irritating**. In a fairly strong solution, on the skin, it causes **blisters** and on the mucous surfaces, **corrosion**. It was sometimes used to cauterise septic wounds. The vapour even in 100,000 dilution, causes marked irritation of the conjunctiva and the respiratory passages.

IODUM (*Iod.*), Iodine

This is obtained from the ashes of certain sea-weeds and also from natural iodides and iodates. It occurs in octahedral flakes or rhombic prisms with a metallic lustre, heavy, bluish black in colour having a peculiar smell. Contains not less than 99.5% of I.

Very sparingly soluble in water but freely so in aqueous solution of potassium iodide and also in alcohol (90%), chloroform and ether : soluble in glycerin.

Incompatibles.—Metallic salts, mineral acids and alkalies, tannic acid, alkaloids, volatile oils and starch. Oil of Turpentine and ammonia form explosive compounds.

OFFICIAL PREPARATIONS.—(i) **Liquor Iodi Aquosus** (*Liq. Iod. Aquos.*), *Lugol's solution*. It contains 5% w/v of iodine or in 15 min. 4/5 gr. of iodine. Dose, 5 to 15 minims or 0.3 to 1 ml. (ii) **Liquor Iodi Fortis** (*Liq. Iod. Fort.*), Strong Tincture of Iodine. (1/11 gr. of iodine in 1 min. or 10% w/v of Iodine). (iii) **Liquor Iodi Mitis** (*Liq. Iod. Mit.*), Weak Tincture of Iodine. (1/44 gr. in 1 min. or 2.5% w/v of Iodine). Dose, 5 to 30 minims or 0.3 to 2 ml.

Pharmacology [and Therapeutics]

Iodine exists in nature in various sea-weeds, sea water and in animals, especially in cod-liver oil. It is essential for the normal working of the thyroid gland. The minimum daily requirement is about 0.5 mg. for an adult human being.

Iodine is one of the **oldest antiseptics** being probably came into use in 1873. In spite of many new discoveries, it is still largely used.

APPLIED EXTERNALLY, it is a powerful **antiseptic** and **deodorant**, elemental iodine having the phenol coefficient of about 200 for *all bacteria without selective action*. On account of its penetrability, the weak liquor is frequently applied on the line of the skin incision in a surgical operation. A 2% iodine in 70% alcohol applied on a gauze padding for two minutes may also do. The same is also applied directly into many septic wounds. A 60 minims of the weak liquor to a pint water is frequently used for douching septic cavities. Iodine and its preparations are **fungicide**, **amœbicide** and moderately **viricide**.

How iodine acts is not quite obvious : probably like chlorine, it *iodises* and *oxidises* chemically the active elements of bacterial protoplasm. Iodamines formed is insoluble and does—

not readily volatilize and so the antiseptic action is slower and more lasting.

Iodine stain is removed by a solution of an alkali, carbolic acid or of sodium hyposulphite.

It is an **irritant**, but less than chlorine or bromine producing a sensation of heat and itching. The skin is tinted yellowish brown, the colour gradually fading. It is less volatile and comes in more intimate contact with the tissues; in concentrated form, it slowly **precipitates protein**, forming easily dissociable iodides and iodo-proteins. A part of it enters into the deeper layers of the skin, may be absorbed and ultimately eliminated with the urine. If in a very concentrated solution, it causes **blisters** and even **corrosion**, more in some people than in others. But the pharmacopœial preparations cause a moderate degree of inflammation only, followed by desquamation of the superficial cuticle.

It acts on the subcutaneous cellular tissue, dilating the blood vessels and improving the circulation and also inducing local leucocytosis⁶⁵. It is a popular **rubefacient** favouring the absorption of inflammatory exudates. [It is frequently used in all kinds of inflammatory process, acute and chronic especially of the pharynx⁶⁶, lymphatic glands, joints and of bones⁶⁷⁻⁶⁸].

It is also a **counter-irritant** and is applied on the skin over an area of deep-seated inflammation in the viscera.

ON THE MUCOUS MEMBRANE, it is a much more powerful **irritant**. On the conjunctiva, nose and throat, the vapour causes smarting and increased secretion: if sufficiently strong, it causes marked corrosion. A 1% solution⁶⁹ is occasionally used as inhalation in chronic lung diseases with foetid sputum.

TAKEN INTERNALLY, it causes **gastro-enteritis** with epigastric pain, vomiting and diarrhœa; stools may be hæmorrhagic, even causing collapse. But in minute doses, as one minim of the weak liquor, it sometimes stops vomiting⁷⁰.

- (65) R
Liq. Iod. Mit.
Liq. Ferr. Perchlor.
Glycer. aa. min. 120
To paint the skin for erysipelas.

- (66) R
Mandl's pigment
Iodum gr. 6
Pot. Iod. gr. 12
Ol. Menth. Pip. min. 3
Glycer. ad. fl. oz. 1
For chronic pharyngitis.

- (67) R
Iodum 1
Acid. Oleic. 4
Paraff. Moll. Flav. 10
An absorbent for chronic inflammation (Martindale).

- (68) R
Iodum
Pot. Iod. aa. gr. 4
Phenol min. 4
Glycerinum
Aq. aa. fl. oz. ½
A colourless iodine paint.

- (69) R
Iodum gr. 4
Æther.
Phenol aa. min. 120
Creosot. min. 60
Alcohol (90%) ad. fl. oz. 1
For inhalation.

- (70) R
Liq. Iod. Mit. min. 1
Tinct. Ipecac. min. 1
Aq. Chlorof. min. 120
One every hour for vomiting.

It is absorbed as iodide in combination with protein and produces a certain amount of **iodide action**. [In order to prevent local effects on the stomach, it is given in milk, starting with 5 minims doses of Lugol's solution and the dose is gradually increased. There are advocates for this method of administration especially in tuberculosis of the bones and glands, and it is believed to be more quickly absorbed when given in this way].

Iodine is the essential constituent of the thyroxin : following its therapeutic administration **thyroxin** in the thyroid gland increases more quickly than with the iodides. [It is useful in toxic goitre and is given for about 10 days before performing any surgical operation on the thyroid gland. The patient temporarily improves ; the pulse and the metabolic rate are reduced and he stands the operation better. But if continued for 2 or 3 weeks, the symptoms may be aggravated.

It is believed that hyperplastic thyroid contains little iodine and will readily take up iodine introduced through any channel : this is the rationale of iodine medication. Recently RADIO ACTIVE IODINE (I^{131}) has been found more useful and orally administered in doses $10\mu\text{c.}$ daily not exceeding 1000 to 2000 $\mu\text{c.}$ monthly. This causes more intensive internal radiation than either X-rays or radium. Favourable results have been reported but the correct dose is not as yet accurately known.

Iodine is an alkaloidal precipitant. In emergency from **alkaloidal poisoning**, tincture of iodine which may be near at hand, 1 in 250 solution may be given by stomach tube and removed by gastric lavage.

Sometimes "**iodism**" is caused by its internal administration although this much more commonly follows the administration of iodides. If given in big doses, it may cause severe gastrointestinal irritation.

Iodine solution is sometimes GIVEN INTRAVENOUSLY in graduated doses⁷¹ for the treatment of a **subacute infection** and is probably of some value. But with bigger doses, it causes hæmorrhagic inflammation of the lungs.

POISONING.—Iodine as tincture of iodine is sometimes taken with suicidal intention. The effects depend on the dose and presence of food, as starches, proteins and fats in the stomach which make iodine inactive.

Taken in 1 to 8 ounce dose, especially on empty stomach, acute corrosive gastro-enteritis results causing abdominal pain, profuse vomiting and diarrhoea and shock from tissue damage and loss of fluid. Circulatory collapse follows ending fatally.

Treatment.—Gastric lavage with barley water also sod. thiosulphate in 5% solution ; egg, milk and alkaline drinks. For shock, intravenous injection of plasma and sodium chloride solution.

(71) B

Iodum. gr. $4\frac{1}{2}$

Pot. Iod. gr. 9

Aq. Steril. fl. oz. 1

For intravenous injection. Start with 1 c.c. up to 4 c.c.

SUMMARY.—Iodine is an **antiseptic** and **deodorant** : applied on the skin it is **rubefacient** and **counterirritant** : taken internally, it temporarily improves **thyrotoxicosis**.

Non-official Preparations

IODINE TRICHLORIDE (ICl_3), a yellow solid substance, is a strong antiseptic on account of readily liberating iodine and chlorine.

ENTODON a water soluble iodine compound is given intramuscularly in chronic fibromyositis and arthritis in 1 to 2 c.c. doses.

IODEOL, (0.2 grm. of iodine per c.c.), an electrically prepared colloidal iodine solution, is given intramuscularly.

SYR. IODO-TANNICUS, (Martindale).—Iodine 2 g., tannic acid 1 g., glycerin 20 ml., water 30 ml. and syrup to make 100 ml. In 30 to 120 min. doses, it is given to scrofulous children.

IODEX, **IODOLEP**, Iodine ointments (5%), used as counter-irritant : also prepared with methyl salicylate 5% which is analgesic.

CALSIOD, Calcium ortho-iodoxybenzoate, 0.5 g. tablets 2 to 4 times daily orally after food is used for chronic arthritis.

IODOFORMUM (*Iodof.*), CHI_3

Yellowish, shining small hexagonal crystals or powder with a characteristic smell. It is prepared by the action of acetone on iodine in the presence of potassium carbonate solution (an alkali).

It contains not less than 99% of CHI_3 , freely soluble in all oils, solvent ether and chloroform and 1 in 100 of alcohol (90%) ; but nearly insoluble in water.

OFFICIAL PREPARATION.—**Suppositorium Iodoformi** (*Supp. Iodof.*), 3 grs. of iodoform in each. See p. 55.

Pharmacology [and Therapeutics]

This is the pioneer of many of the iodine preparations sometimes used for the treatment of septic wounds. It has no local action on the skin or the mucous membranes and by itself it is not an antiseptic also. But applied on a wound surface, in contact with decomposing fat and protein, it breaks down and a slow but continuous liberation of elemental iodine takes place. This iodine is generally not enough to perceptibly irritate the wound, although sufficient to prevent the growth of micro-organisms. It is therefore an **indirect antiseptic**.

This and its allied compounds keep the wound surface clean¹² and dry by **diminishing the secretions**. This is in addition slightly **hæmostatic** and **analgesic** also. But some persons appear to have an *idiosyncrasy* and erythematous skin eruptions may develop at the site of its application. Sulphonamides and penicillin have almost replaced iodoform.

- (72) B
Whitehead's Varnish
 Iodoform 4
 Benzoin 4
 Storax 3
 Balsam of Peru 1 and Purified
 Ether 40 for sealing fresh wounds.

ABSORPTION AND EXCRETION.—The liberated iodine may be absorbed as an albuminate or an alkaline salt of it. If applied in large quantity over a wider area especially in a wound exposing fatty tissues, some iodoform is absorbed direct also, causing symptoms of poisoning.

These are (i) in a mild case, a feeling of bad taste and smell, headache, nausea and vomiting. (ii) In severe intoxication, gastro-intestinal disturbances with taste of iodoform, cerebral excitement and delirium follow. The pulse is quickened, the temperature slightly raised and thereafter, cerebral function is depressed with melancholia : occasionally violent maniacal state. These in rare cases are followed by collapse and death.

Although it is nowadays getting unpopular for many reasons, one of which being its bad smell, it was one time largely used for the treatment of **foul sores** with much secretions, [especially venereal⁷³ and also for chronic sinuses and unhealthy wounds⁷⁴. This was combined with bismuth subnitrate or zinc oxide and made into a cream with liquid paraffin⁷⁵]. But sulphonamides and penicillin are preferred.

It is no longer used internally for iodine action.

Non-official Preparations

ARISTOL (Thymol iodide), IODOL (Tetra-iodo-pyrrol), are used as iodoform substitute and have no bad smell.

C. METALLIC ANTISEPTICS

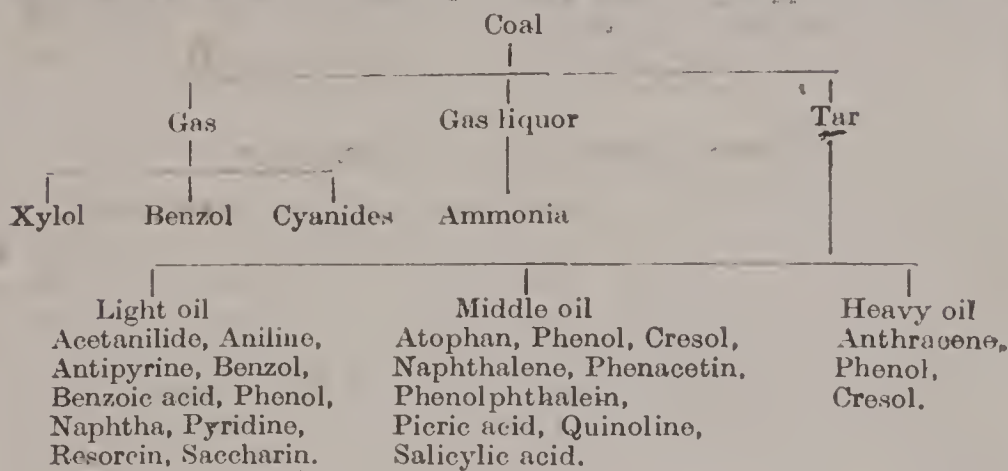
The salts of several heavy metals are used as local antiseptics. The most important of this group are the salts of mercury as perchloride, double iodide, oxycyanide and phenyl nitrate. Copper, silver, aluminum and zinc salts are also used. As these salts have important systemic actions also, they will be taken up in another place.

D. TAR PRODUCTS

These are obtained by the destructive distillation of coal also of pine wood and beech-wood. The products of coal tar are fairly large which is increasing in number and in importance almost daily and of wood tar are mainly oil of turpentine and

| | | |
|------|-----------------------------------|--|
| (73) | R | Acid. Boric aa. gr. 30 |
| | Iodoformum 1 | For insufflation. |
| | Collod. Flex. 12 | (75) R |
| | (Martindale). | Bism. Subnit. 1 |
| | Dissolve. A good paint for vene - | Iodoformum 2 |
| | real sores. | Paraff. Liq. q.s. (B.I.P.P.) |
| (74) | R | To make a thick paste for a chronic wound. |
| | Iodoform | |

creosote. The following table roughly outlines the more important of these from medicinal point of view. (After McGuigan).



TAR DERIVATIVES

1. PIX CARBONIS PRÆPARATA (*Pix. Carb. Præp.*), Prepared coal tar, *Alkatra*.

COAL TAR is a by-product of the destructive distillation of coal and is the mother substance of a vast group of preparations some of which are *antiseptic* as phenol: some are *antipyretic* as antipyrin and others are various *aromatics* and *dyes*.

Prepared coal tar is obtained by heating the commercial coal tar at 50° in a shallow vessel for one hour. Viscous blackish liquid with strong empyreumatic smell. Almost insoluble in water: partially soluble in alcohol (90%) and in solvent ether and freely so in chloroform and benzene. It contains *benzene*, *phenol*, *cresols*, *naphthalene* and many other substances.

Liquor Picis Carbonis (*Liq. Pic. Carbon.*), See p. 50.

2. ICHTHAMMOL (*Ichtham.*), Ichthyol, Ammonium Ichtho sulphonate, fish tar.

This is fish tar and is obtained from bituminous oil stone which contains the fossil remains of fish. It contains ammonium salts of sulphonic acids with 10.5% of sulphur and is partly purified by re-distillation. It is a blackish viscous liquid with a characteristic smell. It is soluble in water, glycerin and fixed oils: partly so in alcohol (90%).

Non-official Preparations

ICHTHALBIN, (Ichthyol with protein), Dose, $\frac{1}{4}$ to 5 grains and ICHTHOFORM, (Ichthyol with formalin), Dose, $1\frac{1}{2}$ to 5 grains, are used as intestinal antiseptics.

3. PIX LIQUIDA (*Pix. Liq.*), Tar, Stockholm tar.

This is obtained by the destructive distillation of wood of various trees of the family *Pinaceæ* (either pine wood or beech wood). Both yield various antiseptics as turpentine, phenol, cresol, creosote, resin and organic acids and the latter has creosote in larger proportion.

It is a semi-solid, brownish black substance with aromatic odour and empyreumatic taste: soluble in alcohol (90%), chloroform, solvent ether and in fixed and volatile oils.

This is in the IND. PHARM. LIST also.

India has an extensive pine area along the Himalayan range from the Punjab and the United Provinces (Almora and Nainital) to Chittagong

hilltracts, the Khasia and the Lushai hills and also to the hills of Burmah. In some places, especially at Chitterbuekgunj (now near about Calcutta also), pine distillation is being done on commercial scale to prepare turpentine, resin and other substances.

OIL OF JUNIPER TAR, (Oil of eade), is a variety of wood tar prepared by distillation of wood of *Juniperus Oxycedrus*. See p. 117.

Pharmacology [and Therapeutics]

TAR was largely used as **astringent, antiseptic, parasiticide and deodorant** for a long time before its more recent products as phenol group were known. It is however less powerful and less poisonous. It is a mild **rubefacient**. [It is used in various acute and chronic skin affections as lotions and ointment ⁷⁶⁻⁷⁷].

Taken Internally with syrup, a little of it is excreted into the lungs and the kidneys and acts as a mild **expectorant and diuretic**. [It is occasionally administered in chronic bronchitis with foetid expectoration and in cystitis but is liable to cause gastro-intestinal irritation].

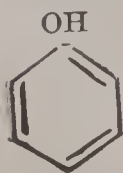
ICHTHYOL on account of its sulphur contents when applied *externally*, is a mild **antiseptic** but slightly **irritant** [and prescribed in various skin diseases, acute or chronic and also to favour absorption of inflammatory products, in watery solution or mixed with glycerin ⁷⁸⁻⁷⁹].

Taken internally, it is a local **antiseptic** and is sometimes given in intestinal fermentation. It **reduces expectoration and cough** in pulmonary tuberculosis, but is liable to upset digestion and its smell is objectionable.

I. COAL TAR PRODUCTS

1. PHENOL, Carbolic acid, C_6H_5OH .

It is obtained from coal tar oil by fractional distillation and subsequent purification or synthetically. It occurs as colourless, needle-shaped, deliquescent crystals, with a peculiar smell of its own and sweetish pungent taste : turns red on keeping for sometime by absorbing carbon dioxide and oxygen from the air due to aurin and rosolic acid present as impurities. It contains not less than 98% of C_6H_5O .



It liquefies at 40° to an oily fluid. It is soluble at 15.5° in 13 of water and freely in alcohol (90%), chloroform, solvent ether, glycerin, oils and fats : with liquid paraffin it makes saturated solution.

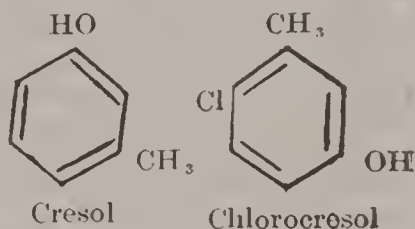
- | | |
|---------------------------|-------------------------------|
| (76) B | Paraff. Moll. Flav. ad. oz. 1 |
| Liq. Pic. Carbon. | Ung., for chronic eczema. |
| Liq. Plumb. Subacet. | (78) B |
| Fort. aa. 2 | Ichthammol 40 |
| Zinc. Oxid. | Glycerin 60 |
| Glycer. aa. 4 | Mix. A paint for erysipelas. |
| Aq. Dest. 36 (Martindale) | (79) B |
| Lotion for eczema. | Ichthammol 25 |
| (77) B | Ext. Bellad. Liq. 5 |
| Hydrarg. Ammon. gr. 15 | Adeps Lan. Hydros. 70 |
| Liq. Pic. Carbon. gr. 30 | For mumps and orchitis. |

OFFICIAL PREPARATIONS.—(i) **Phenol Liquefactum** (*Phenol. Liq.*), Phenol 800 g. and distilled water to make 1000 ml. (ii) **Glycerinum Phenolis** (*Glycer. Phenol.*), about 16% w/w of C_6H_5O . See p. 41. (iii) **Suppositorium Phenolis** (*Supp. Phenol.*), 1 gr. in each. See p. 55. (iv) **Trochiscus Phenolis** (*Troch. Phenol.*), Nearly $\frac{1}{2}$ gr. phenol in each. See p. 61. (v) **Unguentum Phenolis** (*Ung. Phenol.*), 1 in 33 $\frac{1}{2}$. See p. 66.

2. CRESOL, Tricresol, $C_6H_4OHCH_3$.

It is a mixture of cresols and other phenols, obtained from coal tar. It is almost colourless or pale brownish-yellow fluid with a tarry smell which becomes brown on exposure to light. Almost completely soluble in 50 parts of water: freely soluble in alcohol, chloroform, solvent ether, glycerin and in oils.

OFFICIAL PREPARATIONS.—(i) **Liquor Cresolis Saponatus** (*Liq. Cresol. Sap.*), *Lysol*. See p. 49. (ii) **Chlorocresol** is 6-chloro-3-hydroxytoluene, *parachlorometacresol*, C_6H_4OCl , prepared by chlorination of *m*-cresol.



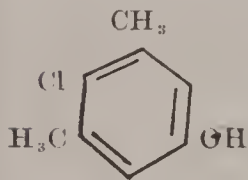
Colourless crystals, with characteristic odour soluble in 250 parts of water at 15.5°, more so in hot water; readily soluble in alcohol (90%), solvent ether, terpenes, fixed oils and sodium hydroxide solution.

3. CHLOROXYLENOL. *Parachlorometaxylenol*,



This is 2-chloro-5-hydroxy-1:3-dimethyl benzene, prepared by the interaction of xylol and sulphuryl chloride.

White or creamy white crystalline powder with characteristic odour. Soluble at 15.5 in 3000 parts of water, more in hot water and freely in alcohol, solvent ether, benzene, terpenes, fixed oils and solutions of alkali hydroxides and in soap.



Liquor Chloroxylenolis (*Liq. Chloroxylenol.*), *Roxenol*.—See p. 49.

TRINITROPHENOL, Picric acid, (Not official).—It is obtained by the action of sulphuric acid on phenol and treating the product with nitric acid. It is a bright yellow powder with no smell but with a bitter taste: soluble 1 in 90 of water and 1 in 10 of alcohol (90%).

Dose, 1 to 5 grains or 0.06 to 0.3 gramme.

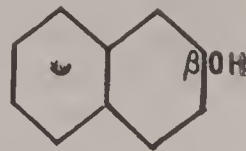
4. BETANAPHTHOL (*Betanaph.*), Naphthol, $C_{10}H_7OH$.

This is beta hydroxynaphthalene obtained by fusion of sodium naphthalene beta-sulphonate with sodium hydroxide and occurs as greyishwhite shining flakes or powder with phenol-like odour and pungent taste.

It is freely soluble in alcohol (90%), solvent ether and in 17 of chloroform but only 1000 parts of water at 15.5°.

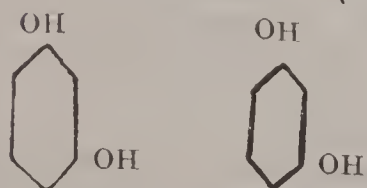
Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

INCOMPATIBLES.—Ferrie chloride, camphor, menthol, phenol and phenazone.



Betanaphthol

5. RESORCINOL (*Resorcin.*), Resorcin, $C_6H_4(OH)_2$.



Resorcinol Hexyl Resorcinol

This is *m*-dihydroxybenzene and obtained by the interaction of caustic soda and sodium-*m*-benzene-disulphonate.

White shining powder or crystals, with a faint odour and sweetish pungent (followed by bitter) taste.

It is freely soluble in water, alcohol (90%), solvent ether, glycerin and to a less extent in oils.

Pharmacology [and Therapeutics]

This group includes phenol, cresol, chloroxylenol, β -naphthol and resorcinol. These are chemically related to one another but are not now so much used as surgical antiseptic.

Benzene is insoluble in water but minus H and plus OH, solubility and antiseptic action is increased making phenol. By the entrance of *alkyl* or *more OH* group to this or by *nitration* or *halogenation*, other compounds have been obtained with greater bactericidal activity.

Cresol, an alkyl derivative of phenol (phenol with substitution of a methyl group) is 3 times more active. *Resorcinal* is phenol with an additional OH : its antiseptic properties are increased by alkyl substitution as in hexylresorcinol or by halogenation. *Trinitrophenol* (picric acid) is by nitration of phenol. Halogenation makes *chlorophenols*, *bromophenols* and *iodophenols* : these are powerful antiseptics but comparatively insoluble in water.

Phenol

Although now-a-days the use of antiseptics in surgery is gradually giving place to various aseptic methods, in the early days of the antiseptic era of Lister (1867), carbolic acid reigned supreme.

Now its use is very much restricted because many newer antiseptics have been prepared which are *more efficient* and *less toxic* both locally and after absorption.

Applied to THE SKIN, it acts as a general **protoplasmic poison** and **coagulates protein**. In a *strong solution* it is therefore a **caustic**. In a *weaker solution*, protein is denatured. As it does not form any firm chemical combination, in case of overaction, the excess can be washed off especially with alcohol. Applied in *concentrated form*, after a brief period of pricking pain, there is **loss of sensation** : the stimulation of the superficial sensory nerve endings is followed by their partial destruction. A white crust is formed which subsequently becomes red and the skin peels off. [In concentrated or in undiluted form, it is used to cauterize the wounds of the bite by a rabid animal : the part is subsequently washed with 95% of alcohol]. In 5% solution, it gives a white tanned appearance to the skin. In *still weaker solution*, when applied as a compress for sometime, it may cause deep dry gangrene appearing insidiously and painlessly, carbolic acid penetrating through the skin. Even 2% solution applied continuously for 2 to 3 days, may do it. It kills the micro-organisms of infection and the tissues of the host in nearly the same dilution and this is its main disadvantage.

On the mucous membranes, the corrosive action is even greater. If a mouthful of the concentrated solution is swallowed, the gastric mucous membrane becomes necrosed just as in poisoning with a concentrated mineral acid.

Its action varies according to the type of the organism. It is more powerful on protozoa (1 in 500 solution being sufficient to stop their movement), less on bacteria and still less effective on bacterial spores and viruses. Although 1 in 500 solution stops the growth of many bacteria, (**bacteriostatic**), 5% solution readily kills them : many spores are also killed but only after 3 to 4 days' contact. The fungi are killed by 1/75 dilution.

It is, however, occasionally used as an **antiseptic** usually in 1% solution, in various septic conditions in the skin, mouth, throat, nose, ear and the genital passages. Its **deodorant** properties make it specially useful⁸⁰⁻⁸⁴. In $\frac{1}{2}$ to 1% solution with calamine, it is an **antipruritic** in irritable skin conditions.

The disinfecting efficiency of phenol has been taken as a standard to estimate the activities of an unknown antiseptic : **phenol co-efficient** (Rideal-Walker method).

Phenol activity depends on its being more **soluble in fat and protein** than in water and so applied in watery solution, it concentrates effectively on the protoplasm of various organisms of infection. It is more **penetrating** than most other coal tar derivatives and metallic protein coagulants.

It is almost *useless in oily solution* as then it remains in physical combination and does not get into the protoplasm of bacteria on the wound surface. Alcohols and glycerin have a similar restraining action. On the other hand, its antiseptic action is increased by addition of a substance that diminishes its solubility in water relatively to that in protoplasm, as sodium chloride, which thus assists its transfer from the solution in which it is applied to the bacteria. Presence of albumin however retards its action by about 10%.

Its power of coagulating protein is helpful in precipitating purulent discharges of an unhealthy wound surface which imprisons the virulent organisms of infection and renders the tissues less permeable and more resistant. It also tends to coagulate blood in the capillaries diminishing the absorption of toxin and lessening exudation.

(80) R
Phenol. gr. 10
Glycer.
Aq. Rose aa. fl. oz. 1 (Lucas).
For Impetigo and Acne.

(81) R
Phenol. 1
Liq. Iod. Mit. 1
Acid. Boric. 2
Aq. Camph. 100 (Lucas).
A gargle or a nasal or uterine
douche.

(82) R
Phenol. gr. 20
Sap. Dur. gr. 20

Orris Pulverata gr. 20
Mag. Carb. Pond. gr. 180
Creta oz. 1 (St. George's) 68
Tooth powder.

(83) R
Phenol. 1
Ol. Ricin. 4
Ol. Amygdal. 20 parts
A catheter oil.

(84) R
Phenol. gr. 2½
Tinct. Opii min. 10
Glycer. ad. fl. oz. 1
An ear-drop. (Royal Free).

It is sometimes injected in 15 to 20% solution into the piles to cause **obliteration of the veins by protein coagulation**⁸⁵. But better pile coagulants are ethanalamine and quinine-urethane.

[For its anæsthetic action, it is often applied undiluted into the cavity of a painful carious tooth. Care should be taken that the soft parts of the mouth are not touched. Phenol with camphor 2 makes an oily liquid which is not very irritant even to the mucous membranes and is an effective anæsthetic].

Although it is now not so much used for dressing wounds, crude phenol still used as a deodorant and disinfectant for room, lavatories, drains, various infected refuse, and the excreta of cholera, dysentery and of typhoid fever. For these purposes, various brands of saponified cresol are however more often used.

In 1 in 20 solution, it may be used for sterilising surgical instruments for a minor operation.

TAKEN INTERNALLY, it checks fermentation in the stomach and is occasionally prescribed as a **gastric antiseptic**. In drop doses, it **controls vomiting** by its local anæsthetic action. It does not destroy digestive ferments in such small doses. But it is seldom used internally. Its salts are however, sometimes used.

ABSORPTION AND ELIMINATION.—Absorbed into the circulation, usually from surgical application, as more commonly happened in the earlier days, when it was more extensively used than now, the toxic effects are mostly shown on the **nervous system**. Drowsiness supervenes, sometimes accompanied by delirium, noises in the ears, deafness, general indisposition, vomiting, great languor, feeble pulse and often profuse sweating and salivation. The heart-rate and the respiration are accelerated probably by its action on the heart muscles and the respiratory centre, but later, these are paralysed. Vasomotor centre is also depressed and the blood pressure falls. Temperature is lowered. Convulsions of spinal type are seen more commonly in a lower animal than in the mammal and seldom in the human being.

Taken orally in large doses, as for suicidal purpose, it causes much local corrosion with severe pain and vomiting and quickly brings about collapse; the face becomes pale, the skin is clammy with cold sweats, the pulse is small and irregular and the respiration laboured. Toxic nephritis also follows and the urine becomes green or even black. Death takes place from paralysis of the respiration.

In milder poisoning, a large portion of the absorbed phenol is oxidised to form hydroquinone and pyrocatechin. These

(85) R

Phenol. gr. 86

Glycer. min. 240

Aq. Dest. ad. fl. oz. 1

2 to 5 minims are injected at a time on each pile.

and the unoxidised portion combine with sulphuric and glycuronic acids and are excreted in the urine: hydroquinone and pyrocatechin are very unstable and, on further oxidation, give a brownish green or almost black colour to the urine. The colour change does not depend on the amount of phenol absorbed but on the quantity oxidised: this toxic action is more common when absorbed from a wound surface.

Glycuronic acid in the urine readuces Fehling solution and so may be mistaken for sugar.

TREATMENT.—The stomach is quickly washed out with warm water or olive or arachis oil (acts as a demulcent also). Shock and collapse are treated symptomatically with stimulants.

SUMMARY.—Phenol is a **caustic, surgical antiseptic** and sometimes used for cauterizing a foul wound or a poisonous bite rarely as a surgical dressing. It is a mild **local anæsthetic** and is used in 1% solution as anti-pruritic and sometimes put inside a painful carious tooth in undiluted form. It is a **sclerosing agent** for piles. But for its **toxicity** both local and systemic, it is now getting out of use. It is often used as **disinfectant** of excreta, sputum, drains, urinals and utensils.

Non-official Preparations

SODIUM AND ZINC SULPHOCARBOLATES.—Are antiseptic owing to their phenol contents. The sodium salt is sometimes prescribed in 5 to 15 grs. doses, as a gastro-intestinal antiseptic. The zinc salt is used as urethral wash in 1% solution.

SALOL, Phenyl salicylate, is sometimes used as a gargle⁸⁶ and internally as an intestinal antiseptic⁸⁷. It acts by dissociating into salicylic acid and phenol in the small intestine. It is also prescribed for its salicylate action in subacute rheumatism and sciatica. It is slightly antipyretic and urinary antiseptic. **DOSE**, 5 to 15 grs.

TRIBROMOPHENOL (Bromol), **DOSE**, $\frac{1}{2}$ to 2 grs. Insoluble powder used as intestinal antiseptic.

DIMOL (Dimethyl-methoxyphenol), in tablets containing 1 gr. or syrup having 0.3 gr. per fluid drachm is a powerful intestinal antiseptic, 3 or 4 such doses being given daily.

SOLOFORM, **TRI-IODOPHENOL**, in 1 to 5% solution are used for vaginal lavage and also as gargle.

Cresol, Acidum Cresylicum

This is phenol with a methyl group added in the benzene ring and is more effective than phenol. Cresol is a mixture of the three isomers, ortho-, para- and meta-cresols; the last is less irritant, less toxic and more powerful than phenol and paracresol is the most toxic of all.

The cresols being insoluble in water are saponified and such an emulsion is a more powerful antiseptic. It comes in more intimate contact with and more soluble in bacterial protoplasm

(86) R
Salol gr. 10
Ol. Menth. Pip.
Ol. Caryoph.
Ol. Cari. aa. min. 2
Alcohol (90%) ad. fl. oz. 1
Gargle, in 4 of warm water.

(87) R
Salol gr. 5
Benzo-naphthol gr. 4
Bism. Carb. gr. 20
Ol. Cinnam. min. $\frac{1}{2}$
Pulv. For summer diarrhoea.

than in water and less readily absorbed than phenol. In 1 in 500 solution, lysol is often used as a vaginal douche. Although the presence of organic matter reduces its efficiency, on account of cheapness, the saponified cresols are largely used for disinfecting sick rooms and lavatories.

It has got a disagreeable odour and is unsuitable for oral administration as gastro-intestinal antiseptic.

CHLOROCRESOL is a fairly powerful germicide without any increased toxicity to the tissue and has a better smell also. It is used as a **preservative** in various preparations stocked for administration by injection.

Non-official Preparations

TRIORTHOCRESYL PHOSPHATE used as food preservative, caused lower motor type of paralysis of the limbs in certain cases.

CRESATIN, acetic acid ester of metacresol, is less toxic than cresol and is sometimes used as ear, nose and throat applications.

CYLLIN, CREOLIN, PHENYLE, HYCOL, IZAL AND TOXOL.—Are various preparations belonging to lysol group.

Chloroxyleneol

This is powerfully bactericidal having Rideal-Walker coefficient of about 36 with low toxicity. Its poor solubility in water is a disadvantage but this is increased by dissolving it in soap solution as in the official liquor.

It is more useful in streptococcal, less so in staphylococcal and almost inactive in several Gram-negative organism infections especially by pyocyanus and proteus bacilli.

This is frequently used for washing many mucous surfaces as gargle and as vaginal douche: with water this makes a white emulsion and 1% solution of it is effective.

This is also used as a *preservative* in 0.1% solution for many pharmaceutical preparations especially those used hypodermically.

DETTOL (Not official) is chlorinated xylenol dissolved in essential oils and neutral soap, frequently used: this has a pleasanter smell and taste.

Beta-naphthol, Naphthol

The action is the same as that of the other members of the phenol group, but it is **less soluble** and **less caustic**. Its vapour is **irritant** to the mucous membranes causing sneezing and coughing on inhalation and a strong solution of it, applied for a long time on the unbroken skin, may cause superficial corrosion and necrosis. In a dilute solution it is an **astringent**⁸⁸.

(88) R

Betanaph. 5

Glycer. 10

Alcohol (90%) 100 (Martindale).

For sweating of palms, soles and axillæ.

It is a more powerful **antiseptic** than phenol. But for its insolubility in water, it is not very much used for this purpose. If applied over a large area, it is easily absorbed from the skin and in the process of excretion through the kidneys, it may irritate the urinary passages causing strangury and pain. In a person with kidney diseases, even an ordinary therapeutic dose may cause toxic nephritis.

It is prescribed for various **skin diseases** as 10 to 25% ointment in conditions suitable for tar. It has a similar action and is much more clean-looking. [Thus it is used for chronic eczema, psoriasis and also parasitic skin diseases like scabies⁸⁹. As it is a local **anæsthetic**, it relieves itching.

TAKEN INTERNALLY, it is a **gastro-intestinal disinfectant** [and is given in chronic dysentery and other bowel diseases⁹⁰. It may cause irritation of the alimentary tract and the kidneys: more rarely disturbances of sight may follow even optic atrophy. It was one time used as **anthelmintic** for hookworm infection in three doses of 15 grains each every hour followed by magnesium sulphate purgative but now obsolete.

It is **excreted** in the urine combined with sulphuric and glycuronic acids which make the urine reddish brown, the colour deepening on further oxidation by exposure to air.

SUMMARY.—Betanaphteol is **antiseptic** and **antipruritic** in skin affections but not so suitable as gastrointestinal antiseptic.

Non-official Preparations

TRINITROPHENOL, Picric acid, coagulates albumin and is used in 1% solution in superficial wounds as burns but if applied over a wide area toxic symptoms may appear and is now hardly used.

ALPHA-NAPHTHOL, although more powerful, is not used as it is more irritant than betanaphthol.

BENZONAPHTHOL, Betanaphthol benzoate, (Dose, 4 to 10 grs.), is safer on account of its less solubility and is therefore preferred orally.

BETOL, Betanaphthol salicylate, (Dose, 3 to 8 grs.), used in cachet for the same action.

NAPHTHALENE, ($C_{10}H_8$), white crystalline masses with a peculiar odour. Insecticide for books and clothes.

Resorcinol

This resembles phenol to some extent but has less **antiseptic** properties: its alkyl derivative as *n*-hexyl is a very potent antiseptic. It is **less poisonous** to the central nervous system, less **caustic** and slightly **anæsthetic**. It is used externally in various skin diseases as **antiparasitic** and **antipruritic** in 2% lotion or 5% ointment: to lessen excessive cutaneous thickening.

(89) R
Betanaph. gr. 120
Sap. Moll. gr. 120
Adeps Benz. ad. oz. 1 (Lucus).
For scabies. To apply after
thorough scrubbing.

(90) R
Betanaph. gr. 5
Bism. Carb. gr. 20
Tannalbin gr. 7½
For chronic dysentery and diarrhoea.

ing and scaling (**keratolytic**) and for promoting the growth of hair⁹¹ either as ointment, dusting powder or as lotion.

It is also used as throat paint⁹² in 5 to 10% solution in glycerin for various painful conditions of throat and tonsils. It is not given internally for gastro-intestinal disinfection on account of its toxicity.

SUMMARY.—Resorcin is *antiseptic, antiparasitic, antipruritic* and *keratolytic* : unsuitable for oral administration.

Non-official Preparations

HEXYLRESORCINOL, *Caprokol*, is taken internally, in 0.15 gm. capsule being a non-toxic and non-irritant *urinary disinfectant*. It is more effective in Strepto. and Staphylococcic than in B. Coli infection. Although one time largely used, sulphonamides have replaced it.

It is also used as an *anthelmintic* for round worm, hookworm, threadworm, whipworm and tapeworm. After a light supper in the previous evening 1 gm. in hard gelatin capsule or in 5, 0.2 gm. pills being given in the morning on empty stomach, no food for at least 4 hours and a dose of sulphate of magnesia is given in the next morning. The children are given a proportionately smaller dose : available as *Crystoid Anthelmintic* in 0.2 gm. and 0.1 gm. pills. These should be *swallowed entire and never chewed*. The results are fairly satisfactory.

Hexylresorcinol solution is a non irritant disinfectant : used undiluted on a wound surface and in 1 in 3 dilution as gargle.

S.T. 37 Antiseptic solution contains hexylresorcinol dissolved in 30% glycerin and 70% water : used for local application or irrigation in 2 or 4 dilution.

EURESOL, Resorcin Monoacetate, a thick liquid is used in 10 to 30% solution in acetone for the same purpose as resorcin.

DYE PREPARATIONS

Various dyes are used as antiseptic. These are : (i) *Azo dyes* : scarlet red and pyridium. (ii) *Acridine dyes* : acriflavine, aminacrine and proflavine. (iii) *Fluorescein dyes* : fluorescein and mercurochrome. (iv) *Rosaniline dyes* : gentian violet, crystal violet, methyl violet, brilliant green and acid violet. (v) *Methylene blue* and (vi) *Phenolphthalein dyes* : phenolsulphonphthalein, iodophthalein.

The action of these tends to follow certain physico-chemical principles. These have been divided into groups, whether the chemotherapeutic radicle is electropositive or electronegative. The former are usually more effective on Gram-positive* and

- (91) B
Resorcin. 5 to 10
Tinct. Capsic. 15
Ol. Ricin. 10
Ol. Rosmarin. 5
Alcohol (90%) 100
Lotio. For alopecia.

- (92) B
Resorcin gr. 30
Phenol gr. 4
Sp. Menth. Pip. min. 30
Glycer. ad. fl. oz. 1
Throat paint.

* Principal **Gram-positive** organisms are (a) *Cocci*, strepto., staphylo., pneumo., *m-tetragens* and *sarcinæ* : (b) *Bacilli* : diphtheria group, acid fast group and spore bearing group. **Gram-negative** organisms are (a) *Cocci*, gono., meningo., catarrh., *melitensis* : (b) *Bacilli* : typhosus, coli., cholerae, *pyocyaneus*, proteus, plague, influenzae and pneumobacilli.

the latter, on Gram-negative organisms. Further, the former act better in basic medium and the latter, on acid medium. Hence these are called either *basic* or *acid dyes*. Of these preparations, fluorescein and phenolphthalein dyes are not used as antiseptics: these are used for diagnostic tests only.

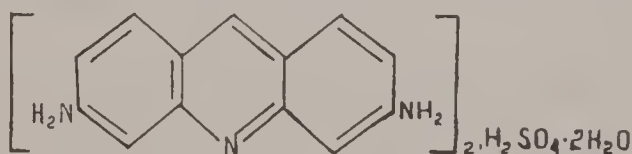
1. ACRIFLAVINA (*Acriflavin.*), Acriflavine Hydrochloride, $C_{14}H_{14}N_3Cl, HCl$.

It is a mixture of the hydrochlorides of 2 : 8-diamino-10-methylacridinium ehloride and 2 : 8-diaminoacridine. Prepared by partial methylation of diacetyldiaminoacridine and subsequent hydrolysis by hydrochloric acid. It contains not less than 95% of total acridines calculated as $C_{14}H_{14}N_3Cl, HCl$.

An orange-red or red crystalline powder, inodorous and acid to taste, soluble at 15.5 in 3 of water, in about 500 parts of physiological solution of sodium chloride: soluble in alcohol (90%) and glycerin; almost insoluble in chloroform, solvent ether, volatile and fixed oils and liquid paraffin.

INCOMPATIBLE with chlorine-containing antiseptics, mercuric chloride and phenol: compatible with normal saline if used within 24 hours.

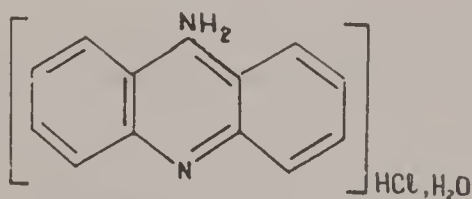
2. PROFLAVINÆ HEMISULPHAS (*Proflav. Hemisulph.*) $(C_{13}H_{11}N_3)_2H_2SO_4 \cdot 2H_2O$, Neutral proflavine sulphate.



Proflavine Hemisulphate

This is neutral sulphate of 2 : 8-diaminoacridine and prepared by heating *m*-phenylenediamine with formic acid and glycerin and converting to hemisulphate with sulphuric acid. It contains not less than 98% of the active substance dried in vacuo at 100°. An orange to red inodorous, hygroscopic crystalline powder with bitter taste. Soluble at 15.5° in 150 of water and in 1 of boiling water: at 20°, in 32 of glycerin: nearly insoluble in alcohol 90% and insoluble in solvent ether and in chloroform. Should be kept in a well-closed container.

3. AMINACRINÆ HYDROCHLORIDUM (*Aminacrin. Hydrochlor.*), $C_{13}H_{10}N_2HCl, H_2O$.

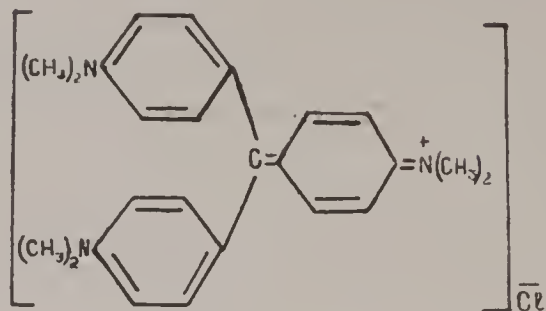


Aminacrine Hydrochloride

Aminacrine Hydrochloride is 5-aminoacridine hydrochloride monohydrate, prepared by treating *N*-phenylanthranilic acid with phosphorus oxychloride and treating this with ammonium carbonate in phenol. Contains not less than 95% of $C_{13}H_{10}N_2HCl$, the substance being dried at 120°.

A pale yellow crystalline inodorous powder with a bitter taste. Soluble at 20° in 300 parts of water and soluble in alcohol (90%) and in glycerin. Saturated watery solution has a greenish-blue fluorescence; a very dilute solution has powerful blue fluorescence.

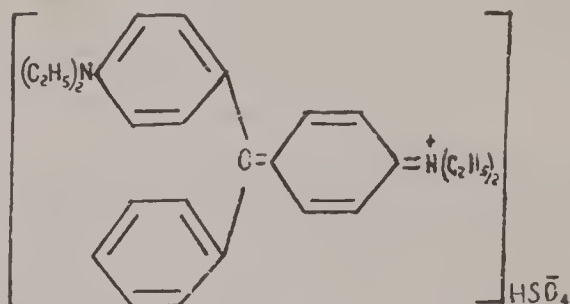
4. **VIOLA CRYSTALLINA** (*Viola Crys.*), Crystal Violet, Medicinal Gentian Violet, $C_{25}H_{30}N_3Cl$.



Viola Crystallina

Crystal violet is hexamethyl pararosaniline hydrochloride prepared by the action of dimethylaniline on tetramethyl-diaminobenzophenone chloride. It contains not less than 96% of pure crystal violet. Nearly inodorous greenish-bronze crystals or powder, soluble at 15.5° in 150 of water, very soluble in alcohol (90%) and in 30 of glycerin: soluble in chloroform but not in solvent ether.

5. **VRIDE NITENS** (*Virid. Nit.*), Brilliant Green, $C_{27}H_{34}O_4N_2S$.



Viride Nitens

Brilliant Green is di(*p*-diethylamino)-triphenyl-carbinol anhydride, prepared by oxidising the condensation product between diethylaniline and benzaldehyde and converting it into sulphate. It contains not less than 96% of pure brilliant green, dried at 110° .

Pharmacology [and Therapeutics]

ACRIFLAVINE, PROFLAVINE AND AMINACRINE

The acridine dyes are yellow in colour and hence called *flavines*. Acriflavine is a powerful **antiseptic** and has several advantages: (i) It acts on the bacteria in high dilution. (ii) It is non-toxic and non-irritant and does not affect phagocytosis in such dilutions. (iii) It is not inactivated (rather intensified) by albuminous exudates of the wounds and (iv) if absorbed, toxic effects are not too serious. But its action is rather slow as the dye takes a little time to penetrate into the bacteria. These dyes are more effective against *Gram-positive* than on the *Gram-negative* organisms and in a slightly *alkaline*

medium (hence called basic dyes). Acriflavine has been found to be 20 times more powerful than mercuric chloride and 800 times more than phenol or chloramine against staphylococcus. The hydrochloride is slightly acid in reaction and acridine base (neutral acriflavine) being neutral and non-irritating, is preferred.

With 10% serum, its antiseptic activity is increased about 100 times but that of phenol, lost 10% and of mercuric chloride lost 90% and this is its main speciality.

Eggerth found that this potentiation of acriflavine by serum *in vitro* was due to the fact that fluid became quite alkaline as CO_2 was given off, and the "basic" dyes acted best in alkaline medium. If precautions are taken to prevent loss of carbon dioxide from the medium, no potentiation takes place.

[A freshly prepared 1 in 1000 or a weaker solution in normal saline is used for irrigating various mucous surfaces or for dressing surgical wounds: the wound cavity is packed with gauze soaked in the lotion and evaporation prevented. This is kept for several hours.] It is a very valuable non-toxic antiseptic and largely used.

The solution should be freshly prepared and one over a week old should not be used. If prepared in normal saline, it is precipitated after 24 hours. It stands boiling and autoclaving. It should be stocked in amber-coloured bottles. The stain is removed by washing with dilute hydrochloric or sulphurous acid solution.

TAKEN INTERNALLY in doses of 0.1 grm. by the mouth, 3 or 4 times daily or intravenously, it is a urinary antiseptic acting more in alkaline than in acid urine. It is also given in other bacterial infections. But the results are not very dependable. Toxic symptoms as bitter taste in the mouth, nausea, congestion of the face, urticaria and syncope sometimes follow. Repeated use causes damage to the liver and kidneys.

PROFLAVINE HEMISULPHATE is neutral proflavine and produces nearly neutral solution. It is more useful in the treatment of discharging newly infected wounds. It is now more frequently used than other acridine dyes in 0.1% solution in various infective processes in the skin, mouth, throat, ear and in genital passages: in 0.025 to 2% solution is used in ophthalmology. Having synergistic action with sulphonamides, 1% of proflavine hemisulphate with sulphathiazole is used as dusting powder on septic wounds.

AMINACRINE is nonstaining, nonirritant flavine antiseptic of low toxicity. Watery solution is stable to heat and light. It is well tolerated by delicate tissues and useful for eye and oto-rhino-laryngological application. It is suitable for surface application both for prophylaxis and treatment as powder or lotion also by intramuscular infiltration in 0.1% solution.

Orally given along with potassium citrate is often useful in cystitis. It is specially active against *B. proteus* and *Gram positive organisms*.

SUMMARY.—Acridine dyes acriflavine, proflavine hemisulphate and aminacrine act best in alkaline medium on Gram-positive organisms in 0.1% or even weaker solution : non-irritant, non-toxic and not inactivated by protein. Penicillin is a powerful competitor.

TRIPHENYLMETHANE or rosaniline dyes are basic in reaction. This group includes *crystal violet*, *gentian violet* or *methyl violet* : *brilliant green* and *fuchsin* : the last is not used medicinally.

Applied Externally, these dyes are **bactericidal** to Gram-positive micro-organisms in nearly 1:10,00,000 dilution, being especially useful against staphylococci, *B. diphtheriæ* and against *B. pyocyaneus* : also the causative organisms of Vincent angina, monilia, epidermophyton and trichophyton. [For direct application 1:500 or 1:1000 ; for instillation in closed cavities 1:10,000 solution may be used]. On the other hand, Gram-negative organisms are very resistant. Acid-fast organisms are also resistant.

Crystal violet (1%) and brilliant green (0.1%) are now much used as lotion, often the two combined. Pigments made in combination are also often used. These dyes form a coagulum with necrotic tissue. This property is of much value for the treatment of burns.* *Triple dye* is sprayed into the burnt area after surgical cleaning : when dry, applied again. Gentian violet may be used as a *jelly* (1%) with tannic acid or alone with tragacanth (Gentian violet jelly B.D.H.). A crust is formed and the wound underneath readily heals. The scar tissue formed is soft and subsequently, does not very much contract.

Internally, Crystal violet is used as **anthelmintic** of choice for strongyloid infection. A dose of 30 to 60 mg. in enteric capsules is given 3 times daily before meal until about 3 g. is reached or this may be given for 8 days : interval for a week and again for 8 days. It is fairly effective in thread worm infection also. It may cause nausea, vomiting and diarrhoea. So in conditions of gastro-intestinal catarrh and in gross cardiac, renal and hepatic diseases, this should be used with caution. Vitamin B complex preparations should also be given during this treatment as crystal violet suppresses the normal synthesis of the vitamin.

Available in $\frac{1}{2}$ gr. (30 mg.) "Enseals" (Enteric sealed tablets) : also a $\frac{1}{6}$ gr. and $\frac{3}{4}$ gr. tablets.

It is sometimes given intravenously in septicæmia and when strongyloids have invaded the lung tissue but is not safe.

* **PIGMENTUM TINCTORIUM B.P.C.**—Brilliant Green and crystals violet 5 g. each, alcohol 90%, 500 ml. and water to 1000 ml.
PIGMENTUM TRIPLEX, Triple dye B.P.C. : Brilliant Green and crystal violet 2.29 g. each, proflavine hemisulphate 1.14 g. and water to 1000 ml.

SUMMARY.—Crystal violet and brilliant green are effective nontoxic antiseptics on Gram-positive organisms. Being protein coagulant these are especially useful in burns. Crystal violet is anthelmintic in strongyloid and oxyuris infections.

Non-official Preparations

EUFILAVINE is diaminomethylacridine chloride, used as lotion locally for irrigating septic wounds : orally in $\frac{1}{2}$ to 1 gr. enteric coated tablet as urinary antiseptic and also intravenously in 1 in 1000 to 1 in 2000 solution, 50 to 100 c.c. for lymphangitis, tubercular adenitis and various septic processes. *Planacrine* is euflavine throat lozenge. *Gonacrin*, 5 mil. of 2% solution of euflavine intravenously or $\frac{1}{2}$ gr. tablet orally is sometimes given for gonorrhœa.

FLAVAZOLE is proflavine 2% and sulphathiazol 98% and **THIAZAMIDE**, sulphathiazol with 1% proflavine or aminoacridine hydrochloride are used for dusting a fresh clean or a suppurating wound.

MALACHITE GREEN is sometimes used in dressing wounds in 1% aqueous solution : for mycotic infection, fresh 2% solution in alcohol 80% with 2% mercuric chloride is sometimes used.

RIVANOL (an acridine dye), a yellowish powder is also similarly used : occasionally with success, as bowel wash (1 in 2000 solution) in chronic dysentery.

CONGO RED, 10 c.c. of 1% solution is given intravenously for hæmoptysis or epistaxis, may be repeated every 5 hours : said to stimulate the reticulo-endothelial cells, activate thrombogen, increase blood platelets and hasten coagulation of blood : the effects disappear in 24 hours.

SCARLET RED, insoluble in water, is used as 2 to 8% ointment to stimulate the growth of epithelium of a clean granulating wound, sometimes used as dusting powder with talc.

CHINOSOL a yellow crystalline powder, 5 to 15 grs. in a pint of water, is a powerful non-irritating antiseptic.

NEOTROPIN AND PYRIDIUM, are compounds of pyridine, (azo dyes), are urinary disinfectants : given in 0.1 gm. tablets, 2 tablets 3 times daily or more, in pyelitis, pyelo-nephritis and cystitis : act both in acid and alkaline urine. Pyridium is a urogenital analgesic. Not to be given in nephritis, acute hepatitis and in uræmia.

Other frequently used *Dye compounds* are methylene blue, indigo carmine, fluorescein, iodophthalein, phenolphthalein, atebirin and red prontosil. These are described elsewhere.

FUSCHIN, basic, is sometimes given in 0.1 g. dose every 10 minutes up to 1 to 2 g. in cholera with benefit. (Basic fuschin has specific action on *V. cholerae*).

PROPAMIDINE ISETHIONATE as jelly or cream (0.15%) is useful in septic wounds and burns : not inhibited by protein and especially useful in streptococci, staphylococci and gas gangrene infections.

TOLUIDINE BLUE, 3 mg. kg. intravenously and repeated in three days has been found of value in thrombopenic purpura, in acute bone marrow suppression and to counteract overaction of heparin.

DINITROCRESOL in 0.5 to 1 mg. per kilo body weight dose is given to increase the basal metabolism for reducing the body weight. Toxic symptoms appeared if the rate exceeded +50.

S.U.P. 36, urea compound of aminobenzoylaminonaphthol and sodium sulphonate, 0.01 gm. in 1 c.c. ampoules, is given intramuscularly in various pulmonary infections. **S.U.P. 468**, a similar combination, in 0.001 to 0.003 gm. per c.c. ampoules is used for acute arthritis, puerperal septicæmia and erysipelas.

OTHER COAL-TAR PRODUCTS

BENZENE, prepared from light coal-tar oil, is applied locally to kill lice : given internally in 20 to 60 minim doses for reducing the number of leucocytes in leukaemia but the results are not very satisfactory.

II. BEECH TAR PRODUCTS

CREOSOTUM (*Creosot.*) CREOSOTE, Creasote.

This is obtained by the distillation of wood tar. It is a mixture of *phenols*, chiefly *guaiacol* and *creosol*; a colourless or yellowish liquid with a peculiar penetrating smell and burning taste. It explodes with silver oxide. Freely soluble in alcohol (90%), chloroform, solvent ether, fats and slightly in water.

DOSE, 2 to 10 minims or 0.12 to 0.6 ml.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY in concentrated form it is **caustic** and in dilute solution, **astringent**. It is probably a more powerful **antiseptic** than phenol and is less toxic especially to the nervous system. But on account of its insolubility in water, it is not much used except by inhalation as **pulmonary antiseptic**. [A few drops of it mixed with compound tincture of benzoin may be used as inhalation^{u3} with steam in acute bronchitis]. Because of its strong odour, it is a **deodorant** [and is useful in removing the bad smell of ozæna, fœtid bronchitis advanced tuberculosis, abscess and gangrene of the lung, being used on Yeo's inhaler^{u1}]. It also relieves the irritating cough. It is a **local anæsthetic** and relieves pain. [So it is sometimes applied into the cavity of a carious tooth with a pellet of cotton wool].

TAKEN INTERNALLY, it is **irritant** to the stomach and may upset digestion and is not now-a-days much prescribed. In $\frac{1}{2}$ to 1 min. doses, it stops gastric fermentation and by its **antiseptic** action allays vomiting^{u5}. But *large doses cause* nausea, vomiting, abdominal pain and diarrhœa.

It is rapidly absorbed and eliminated mainly in the urine as sulphate of guaiacol and creosol. A small quantity is excreted by the breath also and the remainder is oxidised.

It was formerly popular for the treatment of pulmonary tuberculosis and other pulmonary infections. But the quantity of it excreted into the lungs is too small to have any specific effect. It may be of some value in fœtid bronchitis and in pulmonary cavities but should never be given to people with poor digestion and suffering from active pulmonary diseases

- (93) R
 Creosot. min. 60
 Ol. Eucalyp. min. 120
 Tinct. Benzoin. Co. ad. fi. oz. 1
 A few drops are put in Maw's inhaler or a narrowmouthed jug containing boiling water and the fumes inhaled.
 (94) R
 Formalin min. 10
 Menthhol gr. 10
 Creosot.

- Ol. Terebinth.
 Sp. Chlorof.
 Alcohol (90%) aa. min. 120
 To inhale in Yeo's inhaler.
 (95) R
 Creosot. min. 1
 Benzocain gr. 1
 Cerii Oxalas gr. 2
 Cera Flav.
 Sap. Animal. aa. q.s.
 Pil. A gastric sedative for vomiting.

and never in large doses. The carbonate of creosote is preferred. If continued fairly long, in the process of its excretion through the kidneys it may give rise to albuminuria.

Non-official Preparations

CREOSOTE CARBONATE, *Creosotal*, is sometimes prescribed in influenza⁹⁶. It is often better tolerated than creosote being nearly inodorous and tasteless and is sometimes prescribed for influenza and subacute bronchitis.

PROPOSOTE, passes through the stomach unchanged and creosote is liberated in the intestine in the alkaline medium : given in 10 min. capsules as intestinal antiseptic.

GUAIACOL. — Prepared synthetically or from distillation of wood tar creosote. Dose, 5 to 10 minims. It is an *antiseptic* but is seldom used as such. Rubbed into the skin, it causes slight *diaphoresis* and *reduces inflammation* and also temperature. So it is sometimes applied on painful inflamed lymphatic glands⁹⁷. It is not usually given internally orally. It is however sometimes given intravenously, 0.3 to 0.6 gm. dissolved in 2 c.c. of 95% ethyl alcohol and diluted with 18 c.c. of 1% solution of sodium iodide, for *lung abscess*.

GUAIACOL CARBONATE, *Duotol*, (5 to 15 grs.), is a tasteless, insoluble powder : given by the mouth, has less local action on the stomach than creosote and is therefore often preferred⁹⁸.

It is slowly changed in the intestine into an active antiseptic substance. So it is an intestinal antiseptic also.

GUAIACOL BENZOATE, *Benzosol*, 4 to 12 grs. : CAMPHORATE, 5 to 10 grs. ; CINNAMATE⁹⁹, *Styracol*, 5 to 15 grs. are given in cachet or in powder form. POTASSIUM GUAIACOLSULPHONATE, *Thiocol*, 5 to 15 grs., is soluble in water and may be given either in mixture¹⁰⁰ or as powder. These were believed to be pulmonary antiseptic like creosote without much upsetting the digestion.

E. MISCELLANEOUS ANTISEPTICS

ACIDUM BORICUM (*Acid. Boric.*), H_3BO_3 , Boric acid, Boracic acid

Prepared by the action of sulphuric acid on native borates.

White crystals or powder with slightly acid and bitter taste and sweetish after taste, soluble at 15.5° in 25 of cold and in 3 of boiling water, in 4 of glycerin and in 30 of alcohol (90%). It is made more soluble by adding borax. It should contain not less than 99.5% of orthoboric acid.

Dose, 5 to 15 grains or 0.3 to 1 gramme.

It is an ingredient of *Cataplasma. Kaolin.* and *Liq. Sod. Chlorinat Chir.*

- (96) R
Creosot. Carb. min. 10
Mucil. Acac. q.s.
Syr. Tolu. min. 60
Aq. Camph. ad. fl. oz. 1

- (97) R
Guaiacol 1
Adeps Lan. Hydros. 5
Paraff. Moll. Alb. 2
Ung. For mumps and orchitis.

- (98) R
Guaiacol Carb. gr. 5
For pulmonary tuberculosis.

- (99) R
Styracol gr. 10
Salol gr. 4
Lactosum gr. 5
Pulv. For intestinal tuberculosis.

- (100) R
Thiocol gr. 5
Syr. Calc. Hypophosph.
Syr. Tolu. aa. min. 60
Aq. Camp. ad. fl. oz. 1
For chronic pulmonary diseases.

OFFICIAL PREPARATIONS.—(i) *Glycerinum Acidi Borici* (*Glycer. Acid. Boric.*), See p. 41. (ii) *Unguentum Acidi Borici* (*Ung. Acid. Boric.*), 1 in 100. See p. 62.

Non-official Preparations

BOROLYCEIN, Boric acid mixed by heat with an equal part of glycerin. For local application in the mouth.

BOROLIN AND BOROFAX are emollient boric acid ointments in sterile base.

BORAX, (*Borax*), Sodium Borate (*Sohaga*), $\text{Na}_2\text{B}_4\text{O}_7, 10\text{H}_2\text{O}$

Borax is prepared from native borax or by boiling native calcium borate with sodium carbonate solution: transparent, colourless crystals or white powder, inodorous and is slightly alkaline in reaction. It contains between 99 and 103% of $\text{Na}_2\text{B}_4\text{O}_7, 10\text{H}_2\text{O}$. It is soluble 1 in 25 of cold water, freely in glycerin but not in alcohol (90%).

DOSE, 5 to 15 grains or 0.3 to 1 gramme.

OFFICIAL PREPARATION.—*Glycerinum Boracis* (*Glycer. Borac.*), 12%. See p. 41.

Pharmacology [and Therapeutics]

Boric Acid is a feeble acid and Borax a mild alkali. As their action is the same, this not due to either acidity or alkalinity. On the unbroken skin these have practically no action at all. These are feeble antiseptics but not disinfectants. A 2.5% solution stops the growth but does not kill the bacteria. Their special advantage is that these are non-irritating.

[Boric acid is therefore frequently prescribed as a dusting powder¹⁰¹ or in lotion either with water, glycerin or alcohols for the eyes¹⁰², mouth¹⁰³⁻¹⁰⁵, nose¹⁰⁶ and ears¹⁰⁷. It is also

- | | |
|-------------------------------------|------------------------------|
| (101) R | Alcohol (90%) 250 |
| Acid. Boric. 1 | Aq. ad. 1000 |
| Zinc. Oxid. 2 | (Filtered through tale). |
| Pulv. Amyl. | Resembles <i>Listerine</i> . |
| Talc. in equal parts. | (105) R |
| Astringent dusting powder. | Borax gr. 3 |
| (102) R | Pot. Chloras gr. 6 |
| Acid. Boric. gr. 10 | Tinct. Myrrh. min. 5 |
| Zinc. Sulph. gr. 2 | Aq. Dest. ad. fl. oz. 1 |
| Aq. Dest. ad. fl. oz. 1 | A gargle (St. Barth). |
| Eye lotion. | (106) R |
| (103) R | Sod. Bicarb. 13.7 |
| Glycer. Acid. Boric. min. 120 | Borax 13.7 |
| Tinct. Myrrh. min. 60 | Phenol 5.2 |
| Aq. ad. fl. oz. 1 (<i>Lucus</i>). | Glycer. 250 |
| For stomatitis. | Aq. Dest. ad. 1000 (B.P.C.) |
| (104) R | For nasal spray or douches. |
| Acid. Boric. 20 | (107) R |
| Acid. Benz. 1 | Acid. Boric. gr. 20 |
| Thymol 1 | Liq. Plumb. Subacet |
| Eucalyptol 0.25 | Fort. min. 10 |
| Ol. Menth. Pip. 0.5 | Glycer. min. 120 |
| Ol. Gaultheria 0.25 | Alcohol (60%) ad. fl. oz. 1 |
| Ol. Thym. 0.3 | Ear drop. |

used for irrigating the lower bowels, bladder and genital passages of both sexes, various wound surfaces and sinuses. *Mel boracis* (powdered borax 100, glycerin 50 and honey 850), is a domestic remedy for stomatitis. Boric acid in solution is used as hot compress. For this purpose, a 2 to 4% solution is usually employed. Cotton wool (15 to 20%) and gauze (10 to 15%), impregnated with it, are very largely used as surgical dressings. A 4% sterile boric ointment makes a good non-irritating application for a healing wound surface. But if applied over a big surface, may by absorption cause toxic symptoms.

Both were used as **preservatives** for such articles of diet as meat, fish, milk, butter and also in making tinned food. The advantage is that these are almost tasteless and cheap but the disadvantage is the toxic symptoms that may sometimes follow.

TAKEN INTERNALLY, Boric acid and borax are **gastro-intestinal irritants**. Given in a smaller dose these are rapidly absorbed from the intestine and have no local antiseptic action. They do not affect metabolism but given in larger doses, **increase nitrogenous elimination** in the urine. Boric acid is rapidly eliminated unchanged by the kidneys and makes the urine acid. Borax makes the urine slightly alkaline. Both boric acid and borax are mild **urinary antiseptics**. As the excretion is slow, cumulative poisoning may follow.

But many newer urinary antiseptics are much more powerful and safer and have replaced them. [In 10 grs. doses, 2 or 3 times daily, these are sometimes prescribed with hexamine for cystitis¹⁰⁵].

As the rate excretion is rather slow, traces of it being obtained in the urine even after 5 days, its prolonged use may cause **cumulative poisoning** and albuminuria.

Borax was formerly used in epilepsy as a **nerve sedative** but is of no value: on the other hand, may cause toxic symptoms.

If a large quantity of either is taken in orally with preserved food, or when absorbed from an extensive wound surface, serious **symptoms of poisoning** appear.

These are fever, headache, dimness of vision, faintness, vomiting, diarrhoea, irritation of the kidneys and finally considerable prostration, collapse and occasionally death. Papular eruptions and oedematous swelling of the skin are sometimes seen.

SUMMARY.—Boric acid and Borax are mild non-irritant **antiseptics** used on wound surface and on the different mucous membranes. Those as food preservative and urinary antiseptic may cause cumulative poisoning.

(108) R

Acid. Boric. gr. 5

Sod. Benz. gr. 10

Hexamin. gr. 7½

Syrupus min. 60

Aq. Chlorof. ad. fl. oz. 1

A urinary antiseptic.

LIQUOR FORMALDEHYDI (*Liq. Formaldehyd.*),
Formalin, CH₂O

A 37 to 41% w/v aqueous solution of formaldehyde CH₂O with a variable amount of ethyl alcohol, methyl alcohol or both. It is a colourless liquid with characteristic pungent, irritating smell and burning taste. Miscible with water and alcohol (90%).

Pharmacology [and Therapeutics]

Formaldehyde is a powerful **antiseptic** and a useful **disinfectant**, its volatility favouring penetration. The main action is probably reaction between formaldehyde and amino group of the proteins. But the vapour is **very irritating** to the air passages and the eyes, and is consequently unsuitable for general use. In 1 : 200 concentration, it kills most organisms, both spore-forming and non-spore forming, in 6 to 12 hours. A higher concentration is more effective. Its action is probably due to its combining with amino groups in the proteins and also to protein precipitation, effecting a number of other changes (Cushny). [It is occasionally used in $\frac{1}{2}$ to 1% solution as spray for septic throat and in 0.05 to 0.1%, as lavage for vaginal catarrh and endometritis¹⁰⁹, gargle for stomatitis and as injection into a tubercular abscess. It is also added to other volatile antiseptic inhalation¹¹⁰].

But its main use is as **preservative** for zoological and anatomical specimens. Being a protein precipitant, it hardens and preserves the specimens. Dead bodies for dissection are preserved by injecting these with formalin and arsenic. Formalin was used as preservative for milk also, in 1 in 5000 proportion but is not quite safe.

Formaldehyde has the advantage of spreading everywhere and can penetrate clothing, etc., without destroying the colour of fabric and so it is sometimes used for **fumigating** the sick room. The room is closed nearly air-tight and the vapour formed by adding 100 grammes of chlorinated lime to each millilitre of the liquid, is allowed to remain for about 10 hours. An effective sterilization is obtained.

It has important **detoxicating properties**, converting bacterial toxins into toxoids which not causing unfavourable reactions, still retains adequate antigenic properties. Diphtheria and tetanus toxins are made into toxoids: these are used for prophylaxis.

SUMMARY.—Formalin has a **pungent smell** and is a protein coagulating **antiseptic**: mainly used as a **preservative** for pathological specimens and preparation of *toxoids*, occasionally as antiseptic wash and sometimes for fumigation of a sick room.

(109) R
 Formalin min. 15
 Ol. Mentli. Pip. min. 5
 Alcohol (90%) min. 120
 Aq. Dest. ad. fl. oz. 1
 This is added to one pint of hot water for lavage.

(110) Formalin min. 15
 Menthol gr. 5
 Ol. Terebinth.
 Ol. Abiet. aa. min. 90
 Alcohol (90%) ad. fl. oz. 1
 To inhale in Yeo's inhaler.

: Non-official Preparations

FORMOSYL.—Liquid formaldehyde potash soap in 2% solution is a useful antiseptic for irrigation.

PARAFORM.—Solid paraformaldehyde is partly decomposed by heat and used for fumigating rooms, 20 grms. disinfecting 1000 c.ft. Also made into throat tablets, $\frac{1}{4}$ gr. each.

ACIDUM SULPHUROSUM, Sulphurous Acid, H_2SO_3

This is non-official : its preparation *Sodii Metabisulphis* is official.

Sulphur dioxide solution is an **antiseptic** and is sometimes used as throat paint, mouth wash and applied on superficial sores. The fumes as obtained by burning sulphur are used for fumigating sick rooms.

SODII METABISULPHIS. (*Sod. Metabisulphis*), Sodium Metabisulphite, $Na_2S_2O_5$.

SODIUM METABISULPHITE, Sodium pyrosulphate, is prepared by saturating a solution of sodium hydroxide with sulphur dioxide and crystallisation, containing colourless prismatic crystals or white powder, becoming yellow on keeping, with sulphurous odour and acid saline taste. Soluble at 15.5° in 2 parts of water less so in alcohol 95%. This should be stocked in a well-closed container.

It is used in the preparation of *Inj. Adrenal.*, *Inj. Apomorph. Hydrochlor.*, *Inj. Physostig. Salicyl.*, *Inj. Procain. et Adrenal. Fort.*, *Inj. Stibophen.* and *Liq. Adrenal. Hydrochlor.*

This is an **antiseptic** and is sometimes made into a throat paint, 10 grains in an ounce of glycerin. It is also used as a **preservative** for injections and occasionally for foodstuff.

SODIUM THIOSULPHATE, $Na_2S_2O_3 \cdot 5H_2O$ (Not official) is prepared by the action of sulphur on sodium sulphate. Dose, 5 to 15 grains or 0.3 to 1 gramme by subcutaneous, intramuscular or intravenous injection.

CALCIUM THIOSULPHATE in 10% solution, 5 c.c. intravenously or intramuscularly and **MAGNESIUM THIOSULPHATE** tablets orally (for **allergic condition**) are used.

Externally, Sodium thiosulphate is an **antiseptic** and sometimes used as lotion 1 in 10 for ringworm or chloasma and in 1 to 2% solution, as moist applications for burns and dermatitis caused by arsenic and mercury.

INTERNALLY, a thiosulphate is used in arsenic, bismuth and mercurial and sometimes for gold, silver and thallium **poisoning**, by intravenous occasionally intramuscular injections in 0.46 to 1 gm. doses daily. It is also given orally in 2 gm. doses twice daily. Recent introduction of *Dimercaprol* has nearly eliminated thiosulphates.

It is also useful in **cyanide poisoning**. As soon as the diagnosis is made, Sod. nitrite 0.3 to 0.6 gm. in 10 to 15 c.c. of water is given slowly intravenously. This forms methæmoglobin. Following this, 25 grms. of sod. thiosulphate in 50 c.c. is given very slowly intravenously. Methæmoglobin combines with cyanide to make cyanmethæmoglobin which is non-ionisable and non-toxic. Sodium thiosulphate converts cyanide released by dissociation of cyanmethæmoglobin to thiocyanate. This sodium nitrite and thiosulphate treatment is more successful than any other treatment for cyanide poisoning. These can neutralize about 20 times of the lethal dose.

9. ANTIPARASITICS

The following drugs kill various parasites infesting the skin. Each group is useful for a particular kind of parasites.

(i) SCABIES.—Sulphur, beta-naphthol, balsam of Peru, ammoniated mercury, phenol and soft soap. Recently benzyl benzoate and mesulphen (mitigal) have been more preferred.

The action of these have been described in other places.

(ii) PEDICULOSIS (Lice infection).—Cresol, stavesacre, petroleum, ordinary kerosene oil diluted with an equal amount of olive oil, mercurials and oil of sassafras : Betanaphthol, sulphur and balsam of Peru : also insecticides as D.D.T., lauryl thiocyanate, pyrethrum and derris.

For pubic infection.—The affected part is first shaved and cleansed and ammoniated mercurial ointment is rubbed in.

For scalp infection.—After a bath, a towel saturated with oil of Sassafras or Kerosene oil, a solution of mercuric chloride 1 in 2000 of water or 1 in 500 of vinegar should be tied round the head and kept for 12 to 24 hours. After this, the hairs should be washed with soap and hot water and dried. A parasiticide ointment or plain vinegar should again be applied. One such treatment usually succeeds but it may be repeated at the end of a week, if necessary.

Recently D.D.T. in 10% powder or 5% emulsion has been applied on the scalp and the hairs are not washed for 10 days. This kills all lice and their nits.

(iii) RINGWORM (Tinea infection).—Ointments of mercury, salicylic acid, benzoic acid, copper oleate, sublimed sulphur, thymol, iodine and chrysarobin were used. Recently dithranol has been more popular and nearly replaced others.

DITHRANOL Dioxanthranol, *Cignolin*,
Anthralin, $C_{14}H_{10}O_3$

This is 1 : 8-dihydroxyanthranol, prepared by reduction of 1 : 8-dihydroxyanthraquinone. Resembles chrysophanic acid only lacking a methyl group.

An inodorous, tasteless, yellow powder, insoluble in water, slightly soluble in alcohol (40%), in solvent ether, acetone and in benzene. This is available in trade as *cignolin*, *derobin* or *anthralin*.

Unguentum Dithranolis (*Ung. Dithranol.*), 0.1%. See p. 62. The stain from clothes is removed with petrol.

Pharmacology [and Therapeutics]

Its action resembles that of chrysarobin but it is 3 to 4 times stronger fungicide and parasiticide and less toxic and less irritant to the skin and the kidneys. It is also keratolytic (making thick skin thinner). Being a synthetic compound, it can be prepared more exactly and in larger bulk.

[It is applied once or twice daily as 0.5% ointment and on the softer parts as the face, better commenced in 0.25% strength.

Some persons may be hypersensitive to it (allergy) : so a weaker preparation on a small patch of the skin is first tried. But if not causing irritation, the strength may be increased to 3%. It may be used as a paint also dissolved in alcohol or ether. It is useful in ringworm, chronic eczema, psoriasis and alopecia areata].

Non-official Preparations

CHRYSAROBIN AND UNGUENTUM CHRYSAROBIN.—Chrysarobin 4 and simple ointment 96. Were one time largely used for ringworm and psoriasis^{110, 111}. Stain from linen is removed with chlorinated lime.

MESULPHENUM (trade name, *Mitigal*), dimethylthianthene, is used undiluted with vigorous rubbing for 3 successive days for scabies, pediculosis pubis, seborrhœa and acne.

TINEAFAX, an ointment of undecylenic acid is often effective in fungus infection.

SASSAFRAS OIL.—This kills lice and their nits : also applied to ringworm patches with a brush : non-irritant pleasant application, required to continue for a few weeks.

STAPHISAGRIA.—One part of the oil expressed from the seeds added to 6 to 12 parts of almond oil is a good application for pediculosis. An ointment made with the seeds (1 in 5) may be similarly used. But if any open wound is present, toxic symptoms may appear.

THALLIUM ACETATE.—This, calculated as 8 mg. per kilo body weight is given in a single dose orally to children below puberty for ringworm of the scalp. There is rapid and profuse depilation which is complete by the 19th day. New healthy hairs grow again and there is cure. But toxic symptoms and even fatality may sometimes follow. The second dose should not be given within three months.

10. ANTHELMINTICS

Anthelmintics, literally speaking, are drugs capable of killing worms (*G. anti*, against and *helminthos*, worm). In practice, this is used in a more restricted sense meaning mainly the drugs acting on the intestinal worms.

An *ideal anthelmintic* should have a high degree of toxicity for the parasites but much less so for the host. (b) It should not cause much systemic toxic effects. (c) It should be capable of easy administration and pleasant to take. (d) It should not interfere with daily work of the individual. (e) The price also should be moderate.

The parasite may be killed (*vermicide*) or their vitality is so lowered that when a smart purgative is given, these are easily expelled (*vermifuge*).

(111) R

Chrysarobin 5

Acid. Salicyl. 2

Ichtham. 5

Paraff. Moll. Flav. 88

(Unna).

Ung. For ringworm.

(112) R

Æther.

Alcohol (90%) aa. 10

Pyrogallol 1

Chrysarobin 1

Collod. Flex. 120

To apply every 3rd day in psoriasis. (Martindale).

Occasionally, the drug may be slightly absorbed producing toxic symptoms on the host, but these are not usually very much.

In order to bring the drug into intimate contact with the parasites, the bowels should be made fairly empty. It is a good rule to keep the patient on milk diet, give a purgative on the night before and the anthelmintic on empty stomach in the next morning, followed by another dose of purgative 1 to 2 hours after.

With santonin, oil of chenopodium and carbon tetrachloride no preliminary preparation is necessary: these may be given in the morning on empty stomach.

Of the *purgatives*, calomel is best for santonin, the latter requiring bile for efficient action. Castor oil may be used with santonin (See p. 190) and oil of chenopodium but this is not ideal. For most cases, sulphate of magnesium is suitable, half an ounce in 1 fluid oz. of water is given one to two hours after the last dose of the anthelmintic and may be repeated. In any case, the *bowels must be moved adequately* to expel both the worms and the anthelmintics.

The anthelmintics are classified according to their therapeutic effects on different varieties of worms, as follows:

(i) ROUND WORM (*Ascaris Lumbricoides*).—Santonin, oil of Chenopodium, Hexyl resorcinol also to some extent, Carbon tetrachloride.

(ii) THREAD WORM (*Enterobius vermicularis*).—Rectal enema of infusion of vegetable bitters, hypertonic salt solution, solutions of ferric chloride, tannin, soap and of oil of turpentine: Orally, diphenan, hexyl-resorcinol and crystal violet.

(iii) HOOK WORM (*Ancylostoma duodenale* and *Necator americanus*).—Tetrachlorethylene, carbon tetrachloride, oil of chenopodium, thymol, beta-naphthol and hexyl-resorcinol.

(iv) WHIPWORM (*Trichuris trichiura*).—Santonin, hexyl-resorcinol, tetrachloroethylene and oil of chenopodium.

(v) STRONGYLOIDES.—Crystal violet.

(vi) TAPE-WORM.—Filix mas, carbon tetrachloride, pelletierine tannate: cusso, melon-pumpkin seeds and embelia.

(vii) Other worms as FILARIA and various SPIROCHAETES.—These live in the blood and the tissues of the host and are treated by injections of various preparations of arsenic and antimony: for filaria, hetrazen or benocide is more helpful.

LIVER AND LUNG FLUKES are treated by injections of antimony preparations and emetine.

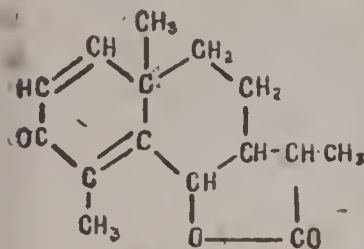
Drugs used in intestinal Helminthiasis

1. OLEUM CHENOPODII (*Ol. Chenopod.*), Wormseed Oil.

Prepared by steam distillation of flowering and fruiting plant of *Chenopodium ambrosioides* in fresh state. It is a colourless or pale yellow volatile oil with bitter taste and characteristic unpleasant smell. It must have at least 65% of *ascaridole*, $C_{10}H_{16}O_2$, the active principle. The weed grows extensively in the United States and hence called American worm seed. Dose 3 to 15 minims or 0.2 to 1 ml.

2. SANTONINUM (*Santonin.*), Santonin, $C_{15}H_{18}O_3$.

Santonin is a crystalline principle in rhombic prisms, colourless and glittering or white crystalline powder obtained from santonica, the dried unexpanded flowerheads of *Artemisia cina*, and other species of *Artemisia*, an annual or perennial herb growing in India in the Western Himalayas, from Kāshmere to Kumaon. But it is usually obtained from Southern Russia. It is also synthetically prepared from naphthalene. It is almost insoluble in water, soluble in $2\frac{1}{2}$ of chloroform, in 40 of solvent ether, and in 50 of alcohol (90%).



Santoninum

DOSE, 1 to 3 grains or 60 to 200 mg.

TROCHISCUS SANTONINI (Not official).—

Santonin (0.06 gm.) with a simple basis (1 gr.) in each.

ARTEMISIA (*Ind. Pharm. List*) is the dried immature leaves or flower heads of *A. brevifolia* and *maritima*. It contains not less than (0.75%) of santonin.

3. DIPHENANUM (*Diphenan.*), $C_{14}H_{13}O_2N$.

Diphenan, *p*-benzylphenylcarbamate, is prepared by the action of ammonia on *p*-benzylphenylchloroformate containing not less than 99.5% of $C_{14}H_{13}O_2N$ dried at 100°.



An inodorous, tasteless white or pale cream crystalline powder almost insoluble in water : slightly soluble in alcohol (90%) and soluble in dehydrated alcohol, chloroform and in solvent ether.

4. CARRONEI TETRACHLORIDUM (*Carbon. Tetrachlor.*), Carbon Tetrachloride, Tetrachlormethane, Tetraform, CCl_4 .

Prepared by the action of chlorine on carbon disulphide. A non-inflammable, colourless, volatile fluid with characteristic smell and burning taste : almost insoluble in water but freely so in dehydrated alcohol, chloroform and solvent ether. It should be kept in a well closed bottle away from light.

DOSE, 30 to 60 minims or 2 to 4 ml. as single dose.

5. TETRACHLOROETHYLENUM (*Tetrachloroethylen.*), C_2Cl_4 .

Tetrachloroethylene is prepared by treating pentachloroethane with milk of lime and purifying by distillation.

A colourless, mobile liquid with a characteristic odour : insoluble in water, soluble in alcohol 90%, solvent ether and in oils.

DOSE, 15 to 45 minims or 1 to 3 ml. This in *IND. PHARM. LIST* also.

6. FILIX MAS (*Filix Mas*), Male fern, *Aspidium*.

The rhizome and frond bases and apical bud of *Dryopteris Filix-mas*, about $\frac{3}{4}$ " (2 c.m.) in diameter, entirely covered by angular, curved, dark brown bases of the fronds which bear membranous scales. It is brown externally, yellowish white or brownish inside. The chief constituent is amorphous *Filicic acid* which is probably the active principle. It contains not less than 1.5% of filicin.

FILICIS PULVIS (*Filic. Pulv.*) is finely made brown powder of male fern.

Extractum Filicis, Liquid extract of male fern. Oil of male fern, oleoresin of *Aspidium* : contain 25% w/w of Filicin. See p. 40.

DOSE, 45 to 90 minims or 3 to 6 ml. Water precipitates the resin which must be given suspended in mucilage or with milk.

7. PELLETIERINÆ TANNAS (*Pellet. Tann.*), Pelletierine Tannate.

This is a light yellow amorphous powder, inodorous but with an astringent taste, being the mixture of the tannates of several alkaloids obtained from the bark of the root and stem of *Punica Granatum*. It contains tannin and two active alkaloids, *pelletierine* and *isopunicine* (quantity between 20 to 24%). It is slightly soluble in water, more freely soluble in alcohol (90%).

The alkaloids were first isolated by Pelletier and named after him.

Dose, 2 to 8 grains or 0.12 to 0.5 gramme.

Pharmacology [and Therapeutics]

OIL OF CHENOPODIUM

This like other volatile oils, is a **gastro-intestinal irritant** and causes burning sensation in the mouth and sometimes vomiting. It is **depressant** to the smooth muscles and also to the muscles of the intestinal parasites. The latter action makes it a successful **anthelmintic**.

This is effective both for the **hook-worm** and **round worm** also **dwarf tape worm**. As some samples of it have been found to be highly toxic and others deficient in the active principle, one standardised to contain 65% of **ASCARIDOLE**, ($C_{10}H_{16}O_2$), the active principle, should be used.

No special preparation of the patient is necessary, only a light meal is given on the previous night. As the oil has a bad smell, burning taste and is nauseating, 1.5 to 2 c.c. of it divided into 2 or 3 doses is given in syrup or in hard gelatin capsules on empty stomach in the morning, one every hour followed 2 hours after, by a purgative of saturated solution of sulphate of magnesium or castor oil. No food should be given till the bowels move well. Children are given one minim of it per year of age up to 12 years with sugar. It is often necessary to give 2 to 3 courses of treatment at intervals of 7 days.

A saline enema containing 2 to 10 minims of it is helpful in **thread worm infection** (Clark). It was used in **chronic amoebiasis** resisting emetine treatment but is of doubtful value and is now almost obsolete.

It is a fairly safe anthelmintic except to a pregnant woman also in cases of severe **anæmia** or when marked **cardio-renal** diseases are present. A diet rich in carbohydrate given a few days before the treatment, increases the tolerance.

It is readily absorbed from the intestine, partly excreted into the lungs (odour detected in the breath) and the rest, oxidised and excreted in the urine.

TOXIC SYMPTOMS.—These may follow a single dose or several smaller doses repeated. These are nausea, vomiting, abdominal pain, dizziness, tinnitus, headache, drowsiness, convulsion, coma and death from respiratory failure. Deafness, albuminuria and hæmaturia are sometimes found.

Treatment.—Saline cathartic should be immediately given also a plenty of fluid for flushing the kidneys: circulatory and nervous stimulants may be necessary.

One of my patients took the oil without medical direction for seven consecutive days, became semicomatose and ultimately developed paresis of the upper extremity. The cerebral symptoms slowly cleared up in 10 days, but the muscles of the shoulder girdle and to a less extent, the same of the upper and forearms got marked wasting of the lower neurone type: there was no disturbance of hearing nor of any other special sense.

SUMMARY.—This oil is effective against *ancylostoma*, round-worm and dwarf tape-worm infections. The patient is given a carbohydrate rich diet for 2-3 days and the drug in gelatin capsules is administered on empty stomach in the morning and 2 hours after, mag. sulph. purgative. *Contraindicated* in pregnancy, severe anæmia and advanced cardiovascular disease.

ASCARIDOL in 4½ grs. perle, one is given 3 times at intervals of 1 to 2 hours followed by a purgative: said to be safe and effective.

The IND. PHARM. LIST Oil of *Chenopodium* is *Oil of Bathu Sag*.

SANTONIN

Santonin is a dependable anthelmintic for round-worm¹¹³⁻¹¹⁴ although moderately effective against thread worm it is not now used as crystal violet is much more effective. Although isolated in 1820 only, the plant itself was in use from a very ancient time.

TAKEN BY THE MOUTH, it has only a slightly bitter taste and capable of easy administration. A part of it is dissolved in the stomach but the rest passes on to the intestine. There it acts in such a way on the worms that these are forced to come down to the lower bowels and if now a dose of rapidly acting purgative is given, these are expelled although many of them may still be alive.

In fact, the worms are so resistant that very few poisons will kill them in situ with a dose safe for the host.

A dilute solution of santonin mixed with bile and an alkali (as sodium bicarbonate) is highly toxic to these worms, causing violent contraction of their ring muscles. Santonin finds both bile and alkalies in the small intestine and probably causes dislodgment of the worms in this way. The best purgative to accompany is therefore calomel which hastens the bile flow into the small intestine.

[No special preparation is necessary. Santonin with calomel is given at bed time after a light evening meal and *not on empty stomach* as this favours absorption. This is

(113) R

Hvdrarg. Subchlor.
Santonin. aa. gr. 1
Phenolphthal. gr. ½
Lactosum gr. 3

Pulv. For a child of 5 years.

(114) R

Santonin. gr. 1
Zingib. gr. ½
Sulphur. Præcip. gr. 2
Conf. Senn gr. 20

For a child of 5 years.

followed by a dose of sulphate of magnesia in the morning. The stool is examined 2 days and again 10 days after for the ova of the worms. If none found, no further treatment is necessary].

Castor oil although dissolves santonin, on account of its rapid purgative action does not allow much of it to be absorbed and is not particularly harmful.

EXCRETION.—It is insoluble in water but is easily soluble in weak alkalies in the duodenum and is readily absorbed. Santonin is partly oxidised in the tissues and is excreted in the urine and faeces in various forms, two such are oxysantonins; with a big dose, unchanged santonin is also found. The urine, if acid, turns deep yellow and if alkaline, pink in colour. Sometimes the urination may be painful causing strangury and even hamaturia. The total excretion takes 2 to 3 days or more.

TOXICITY.—The usual effect of a therapeutic dose (which is almost near to toxic dose) is to cause yellow **colouration of the urine** and disturbances of **colour vision** so that many things look yellow (*xanthopsia*) and blue, green and violet are badly seen. These are due to specific action on the retina. With a bigger dose, there is greater disturbance of vision, especially marked at the violet end of the spectrum so that violet and even blue become indistinguishable from black. In some cases, the sense of smell, taste and hearing may also be affected. All these pass off in a few hours though "violet vision" may continue longer.

TOXIC SYMPTOMS.—When a larger quantity is absorbed, the toxic symptoms are greater. There may be nausea, vomiting, headache and vertigo: with a still larger dose, twitchings of the muscles of the head and neck, grinding of teeth and rolling of the eyeballs and even epileptiform convulsions, all due to stimulation of motor cells of the brain. Finally, there is collapse: the skin becomes cold, pupils are dilated, pulse and respiration become feeble and death follows from failure of respiration. But such a catastrophe is exceedingly uncommon with the usual therapeutic dose. It is however a good rule to give a rather small dose: to a child below 5 years, half to one grain and to an adult, three grains only and to ensure quick working of the bowels.

SUMMARY.—Santonin is popular in **ascaris infection**: usually combined with calomel is given at bedtime (not on empty stomach) and mag. sulph. purgative next morning. Toxic symptoms may follow as therapeutic dose is near to toxic dose.

BUTEA FRONDOSA (*Polash bij*), Not official.—In the form of freshly powdered seeds (DOSE, 30 to 60 grs.) is useful in round worm infection. Old seeds are less effective.

DIPHENAN

Diphenan is an effective drug for infection by **thread worms**, causing their muscular contraction and rapid death. One 0.5 g. tablet is given 3 times daily for seven days followed by a dose

of castor oil. Children are given proportionately smaller dose. The treatment may be repeated one week after.*

Local treatment of the rectum as by various rectal enemas, may be given at the same time.

CARBON TETRACHLORIDE

This was prepared in 1849 and being related to chloroform, was used as *general anæsthetic* by Simpson but soon discontinued on account of its higher toxicity. It was also used in industry as *solvent* for fats, oils and rubber.

Carbon tetrachloride *applied externally* is a local **antiseptic**, **irritant** and **rubefacient** on the skin also on the mucous membranes. It has a pungent burning taste giving a sense of warmth to the stomach. It stimulates intestinal peristalsis.

This was introduced as an anthelmintic by Hall in 1921 and is now more popular than oil of chenopodium. It is more effective on *Necator americanus* whereas oil chenopodium acts best on *anelylostoma duodenale*. The usual dose is 3 min for each year of age up to 15 years to the maximum of 60 min. and given on empty stomach in the morning with water, skimmed milk or in hard gelatin capsules as a single dose. This is followed in one to two hours by a dose of saturated solution of sulphate of magnesia. Fatty food and alcohol are prohibited for several hours after. Its advantages in mass treatment are : (i) no preliminary preparation and suspension of work are necessary, (ii) cheap and not nasty to take, one administration removes not less than 90% of the worms : a second administration should only be after a rest for three weeks, (iii) it is safe and effective.

It is somewhat effective in **thread worm** and **tape worm infections** : the thread worms are killed, the tape worms are somewhat anæsthetised and expelled by the purgative following : but is not usually used for these infections.

A combination of oil of chenopodium 1 c.c. with 3 c.c. of carbon tetrachloride gives a better result¹¹⁵. Such a mixture does not increase the toxicity for the host since ascaridole affects mainly the central nervous system and carbon tetrachloride, the liver. Further, it acts against both varieties of hook worm and also against round worm.

(115) B

Carbon. Tetrachlor. min. 45

Ol. Chenopod. min. 15

Paraff. Liq. ad. fl. oz. 1

To be given in the morning.

1½ hours after, 1 fl. oz. of S.S. Mag.

Sulph.

* *Diphenan* (B.D.H.) and *Oxylan* (B.W.), 0.5 g. tablets are available.

After oral administration, intestinal absorption is not much and no systemic effect is produced. But if allowed to remain in the intestine for sometime especially in the presence of fats and alcohols, a certain amount may be absorbed. So a single big dose followed by a brisk purgative increases the safety.

It is *contra-indicated* in persons with severe anæmia, alcoholic habit and also when gross pathological changes in the liver, kidneys, heart and lungs are present.

TOXIC SYMPTOMS are manifested immediately on the alimentary canal afterwards on the central nervous system, liver and the kidneys.

Often there is a sensation of warmth in the epigastrium and belching; rarely dizziness, headache, somnolence and nausea: even more rarely, fatty degeneration of the liver (somewhat resembling chloroform poisoning). These are best prevented by using chemically pure CCl_4 , a diet rich in carbohydrate and administration of calcium.

SUMMARY.—Carbon tetrachloride alone or with oil of chenopodium is given for *hook-worm* and *round-worm infections* in gelatin capsules on empty stomach in the morning and in 2 hours, mag. sulph. purgative: fatty food and alcohol should not be taken for several hours before and after: *contra-indicated* in severe anæmia, alcoholism and in diseases of liver, kidneys, heart and lungs.

TETRACHLOROÆTHYLENE

The action is much like that of carbon tetrachloride in *ancylostomiasis*. It is probably more effective. It is about $\frac{1}{5}$ th as soluble in water and in the absence of fat, not appreciably absorbed from the intestine. It is therefore less toxic to the liver and the kidneys. Here also a single big dose followed by a saline purgative is safer.

Mode of Administrations—Three or four soft gelatin capsules of 1 ml. each are given one every half hour followed in 2 hours by Mag. Sulph. or Sod. Sulph. purgative: or 3 ml. of the drug shaken up with 2 fl. oz. of saturated solution of Mag. Sulph. is given on empty stomach in the morning and a thorough clearing of the bowels is ensured.

It may be combined with one ml. of oil of chenopodium which expels the round worms also.

TOXICITY.—Occasionally slight dizziness may be complained of indicating absorption but no severe reactions have been reported. The patient is kept in bed and a plenty of fluid administered.

SUMMARY.—Tetrachloroethylene is the safest anthelmintic for hook-worm infection: given on empty stomach in the morning followed by mag. sulph. purgative: may cause transient giddiness.

Tetrachloroethylene is available as 0.5 or 1 c.c. capsules (*Tetracap*, B.W.) and of B.D.H. 1 4 6

FILIX MAS

The oleo-resin is gastro-intestinal irritant and may cause nausea, vomiting and diarrhœa. If absorbed, causes renal irritation during excretion and abortion in a pregnant woman.

This in the form of the official extract is a powerful remedy used almost *exclusively* for tape worm. The active principle, pleoresin is markedly depressant to smooth muscles. This paralyses the parasites and these are removed by the purgative. The patient is prepared beforehand by keeping him on milk diet and Mist. Alba for 2 days so as to empty out the intestine as much as possible. The extract is given either in capsule, of 12 min. each, 5 being given or in emulsion in 3 doses¹¹⁶⁻¹¹⁷ of 20 min. each (for an adult male), one every half hour early in the morning on empty stomach. Two hours after, one ounce of saturated solution of magnesium sulphate is given and a good opening of the bowels ensured. Till then, no food should be given. As the drug is nauseating, the patient must be kept in bed nearly the whole day. When the worm is passed, its head should be looked for. If the head is not there, the treatment should be repeated 7 days after.

The drug should be fresh as it tends to deteriorate on keeping. No oil or alcoholic preparation should be given for several hours after its administration as filicic acid being soluble in these media, tends to get absorbed and cause toxic symptoms.

Its toxic principles being mixed with resin, are not easily absorbed. So with the usual therapeutic doses, it does not cause much toxic symptoms. But sometimes even a moderate dose may do so. These are acute gastro-enteritis, as vomiting and purging with severe gripes, muscular cramps, convulsion leading to muscular exhaustion and death from collapse. Jaundice and optic neuritis even blindness have been found in some cases. These are more common in debilitated anæmic persons and in the alcoholics.

The drug should not be prescribed to a person with gross heart, liver or kidney disease and never to a pregnant woman.

SUMMARY.—Filix mas is used for tape worm infection only. Preliminary preparation with milk diet and alba mixture for two days is followed by the drug in 3 divided doses in succession on empty stomach in the morning followed by mag. sulph. purgative: the head of the worm should be looked for in the stools passed. *Contraindicated* in pregnancy and in advanced diseases of the heart, liver and kidneys.

Non-official Preparations

FILMARON, in capsule (containing aspidinofilicin), 3 are given (a total dose of 1 mg.) at a time or half hourly, followed by a strong purgative.

(116) R

Ext. Filic. min. 60

Mucil. Acac. min. 120

Aq. Cinnam. ad. fl. oz. 1

Divide into 3 doses: one every
½ hour.

(117) R

Aspidium gr. 60

Acac. Pulverat. gr. 30

Aq. Dest. fl. oz. 1

Divide into 2 doses. One to be
taken every hour.

PELLETIERINE TANNATE

This being insoluble in the stomach, passes through it unchanged, into the intestine where it acts as a powerful anthelmintic for **tape-worm** only and one in 10,000 solution is sufficient to kill these worms. The patient is prepared (p. 193) for 2 days also given 30 grains of sodium bicarbonate 3 times daily. About four grains of pelletierine are given on empty stomach in the morning which is followed by a brisk saline purgative. Though toxic symptoms are rare and is comparatively safer, it is not as popular or dependable as *filix mas*.

TOXIC SYMPTOMS are nausea, vomiting and diarrhoea : dizziness, muscle twitching, hyperexcitable reflexes, visual disturbances, followed by muscular paralysis and death from respiratory failure. A saline purgative : also symptomatic measures are necessary.

Non-official Preparations

CUSO, **MELON-PUMPKIN SEEDS** (red gourd seeds), **EMBELIA** (*Biranga*) and **ARECA NUT** have also similar actions on tape worm but are less frequently used.

VERNONIA, *Somraj*.—The fresh dried seeds may be used as anthelmintic for round-worm and thread-worm.

DOSE, 15 to 30 grains or 1 to 2 grammes. (IND. PHARM. LIST).

Anthelmintics for *Veterinary use* in the IND. PHARM. LIST are (a) *Areca* (b) *Phenothiazina*. Phenothiazine is toxic to the round worm and thread worm also to the host and is not to be used on a human being.

11. INSECTICIDES

Insects are responsible for propagation of many infectious diseases as malaria by mosquitoes and typhus by mite. In the same way, sandflies, house flies, lice, fleas, bed bugs and cockroaches are important. In agriculture, insects sometimes attack the vegetables. These pests are required to be killed by cheap and simple substances that are comparatively non-toxic to the human being and to the domestic animals.

A. INSECTICIDES.—The outstanding recent achievement is introduction of *Dichloro-diphenyl-trichloroethane* (D. D. T.)

Although discovered in 1874 by a German research chemist its possibilities as insecticide were made out in 1939-40, and introduced in practice comparatively recently.

It is a multipurpose residual insecticide and not repellent. It is a **contact poison**. The flies or insects are killed even if they touch dry surface of D. D. T. by their feet. The action is slow and for quick action pyrethrum extract may be used : or the two may be combined.

D.D.T. does not stain or injure fabrics and not corrode metal and is not offensive. It is fairly cheap and easily applied. A 5% concentration is usually used either as powder, or in kerosine oil solution. It is applied to the clothing (for cloth moths) and beddings as powder and for other purposes, spraying is convenient as on furniture, walls, vegetations and other

materials out of doors. The surfaces so treated remain lethal to insects for about two months : the drug does not lose potency by sunlight or rains. The breeding places of mosquitoes may be sprayed.

In this way malaria, sand fly fever, leishmaniasis, dengue, trypanosomiasis, typhus, plague and fly-propagating diseases as typhoid and dysentery are controlled.

Being insoluble in water, its toxicity on the human being is nearly absent. A 2% emulsion has been found useful for destroying head lice (p. 184). For scabies, it is probably inferior to benzyl benzoate.

Recently another insecticide, *Benzene hexachloride* (666) is proving very promising.

Gamma isomer of Benzene Hexachloride, *Gammexane* I.C.I., is available ;

(i) "Gammexane" Dust D. 025 diluted 10 times with tale or fine road dust, is dusted or sprayed with a special apparatus for insects in clothes, beddings, walls and in furniture.

(ii) "Gammexane" Dust D. 034 is partially deodorised, is mixed with the food grain which keeps quite well.

(iii) "Gammexane" Liquid concentrate diluted with 30 parts of kerosine oil is sprayed.

(iv) "Gammexane" Smoke generators : in 2 oz. pellet and 1 lb canister. The room is closed almost air tight and the smoke generator is burnt : pellet is sufficient for 2000 cu. ft.

Another similar product is *Hexyclan*. This is available as liquid for spray or as powder. In dilution 1 : 500, it is used for agricultural and in 1 : 150 for domestic use for flies, fleas, ants, mosquitoes, cockroaches and rats.

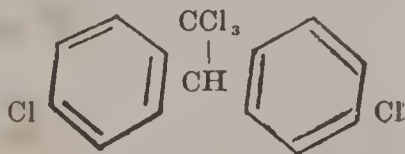
B. INSECT REPELLENTS.—Till lately *Citronella* oil was fairly popular. A few drops applied on the skin or the oil sprayed, was sufficient to keep away mosquitoes and flies but the effects are short staying.

This has been superseded by *Dimethylphthalate* (D.M.P.) Applied on the skin, it gives protection against insect bites for 2 to 3 hours. Exposed parts of the body covered with D.M.P. impregnated veils, gloves and socks are satisfactory. Weekly impregnation is necessary. A 35% cream or lotion may be used.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

1. *Dichloro-diphenyl-trichloroethanum Purum*, $C_{14}H_9Cl_5$, and *Dichloro-diphenyl-trichloroethanum Technicum*, D.D.T. pure and D.D.T. technical.
2. *Cupri Aceto-arsenitum*, Vienna green : Paris green.—This has been used as larvicide of mosquitoes : used on the surface of water by "brush-spray-mop" method. Arsenic poisoning may follow.
3. Insecticides are also obtained from natural sources. These are

(a) *Derris* and (b) *Pyrethrum*,
DERRIS is the dried rhizome and roots of *Derris ferruginea* containing not less than 1% of rotenone. It is used as *Applicatio Derridis* (Derris finely powdered 25, hard soap 6.9 and distilled water to 1000) : should be freshly prepared. It is of special value in agriculture for warble fly.
PYRETHRUM is the dried flower of *Chrysanthemum Cinerarifolium* containing not less than 0.4% of pyrethrin I and pyrethrin II. *Unguentum*



Pyrethri (Pyrethrum 10 and paraffin ointment 90). Pyrethrin 3.3 g. dissolved in 100 ml. of Kerosine oil (*Pyroxide* 40) and *Solutio Pyrethri*, 1% solution of pyrethrin, are used as spray especially against mosquitoes. Pyrethrum may cause dermatitis.

Nippo, a commercial product has D.D.T. with pyrethrum, used as spray.

These are, however, falling into the back-ground and D.D.T. and Benzene Hexachloride are going ahead.

12. DRUGS HAVING LOCAL ACTION ON THE ALIMENTARY CANAL

A large number of drugs has local actions on the alimentary canal, increasing or decreasing the normal *secretions* and also *movements*. Many of these have in addition systemic actions also. These have been discussed in detail in Section XIII of Part 2. Here only those drugs are taken up as have mainly local actions. These include the Vegetable bitters acting as *sialogogues* also drugs that are *digestants* and *purgatives*.

A. SIALOGOGUES, VEGETABLE BITTERS

This group includes 6 drugs as Calumba, Gentian, Quassia, Fresh orange peel, Dried orange peel and Serpentry, all having local action only on the mouth and reflexly on the gastro-intestinal tract. The first 3 are *simple* and the rest, *aromatic* bitters (containing volatile oil).

Drugs as Cinchona, Nux vomica, Cascara Sagrada, Aloes and Rhubarb are also bitter stomachics but these have other important actions also.

(1) CALUMBA (*Calumb.*), Calumba root.

Calumba is the dried and transversely cut root in flat, oval or circular slices, depressed in the centre, of *Jateorhiza palmata*: 2 to 8 cm. in diameter and 3 to 12 mm. in thickness; the cortex is thick and the coat is greyish brown and wrinkled. Its chief constituents are a neutral bitter principle, *calumbin* and alkaloids allied to berberine. It does not contain any tannin and therefore may be given with iron.

CALUMBA PULVIS (*Calumb. Pulv.*) is a fine greyish or yellowish white powder.

OFFICIAL PREPARATIONS.—(i) *Infusum Calumbæ* (*Inf. Calumb.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (ii) *Infusum Calumbæ Concentratum* (*Inf. Calumb. Conc.*), Cold water is used to avoid extracting much starch which is also present in the root. Dose, 30 to 60 minims or 2 to 4 ml. See p. 41. (iii) *Infusum Calumbæ Recens* (*Inf. Calumb. Rec.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (iv) *Tinctura Calumbæ* (*Tinct. Calumb.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 59.

(2) QUASSIA (*Quass.*).

It is a yellowish-white dense, tough and porous wood available in chips from the trunk and branches of *Picræna excelsa* of Jamaica. Its active principle is *Quassin*, a bitter neutral substance. It contains no tannin and can therefore be prescribed with iron.

QUASSIÆ PULVIS (*Quass. Pulv.*).—Pale buff powder of quassia.

THE INDIAN PHARM. LIST variety, *Picræna quassioides*, that grows in Nepal, is an effective substitute.

OFFICIAL PREPARATIONS.—(i) *Infusum Quassiae Recens* (*Inf. Quass. Rec.*) 1 in 100, Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (ii) *Infusum Quassiae Concentratum* (*Inf. Quass. Conc.*) Dose, 30 to 60 minims or 2 to 4 ml. See p. 41. (iii) *Infusum Quassiae* (*Inf. Quass.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (iv) *Tinctura Quassiae* (*Tinct. Quass.*), Dose, 30 to 60 ml. See p. 60.

(3) GENTIANA (*Gentian.*)

Dried rhizome and root of *Gentiana lutea* from Central and South European mountains. Its chief active principle is gentiopicroin, a very bitter glucoside, soluble in water. It contains only a trace of tannin yet it cannot be prescribed with iron as the colouring matter is darkened. Cylindrical yellowish brown pieces with circular leaf-scar and irregular longitudinal furrows: the bark is thick; the fractured surface is reddish yellow.

GENTIANÆ PULVIS (*Gentian. Pulv.*) a light brown or yellowish brown powder.

INCOMPATIBLES.—Iron, Silver and lead salts.

OFFICIAL PREPARATIONS.—(i) *Infusum Gentianæ Compositum Concentratum* (*Inf. Gent. Co. Conc.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 41. (ii) *Infusum Gentianæ Compositum* (*Inf. Gent. Co.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (iii) *Tinctura Gentianæ Composita* (*Tinct. Gent. Co.*), Dose, 30 to 60 minims. or 2 to 4 ml. See p. 59.

(4) AURANTII CORTEX RECENS (*Aurant. Cort. Rec.*), Fresh bitter orange peel.

Outer pericarp of ripe or nearly ripe, *Citrus Aurantium* that grows in India, Eastern Colonies and South Europe. The odour is characteristic, strong and fragrant; taste is bitter and aromatic.

OFFICIAL PREPARATIONS.—(i) *Tinctura Aurantii* (*Tinct. Aurant.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 59. (ii) *Syrupus Aurantii* (*Syr. Aurant.*), Dose, 30 to 120 minims or 2 to 8 ml. See p. 55.

(5) AURANTII CORTEX SICCATUS (*Aurant. Cort. Sicc.*). Dried bitter orange peel.

This is the dried outer pericarp of the above and contains a *volatile oil*, *Oleum Corticis Aurantii* and three bitter *glucosides*.

OFFICIAL PREPARATIONS.—(i) *Infusum Aurantii* (*Inf. Aurant.*), Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. See p. 41. (ii) *Infusum Aurantii Concentratum* (*Inf. Aurant. Conc.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 41.

Dried bitter orange peel is also used in the preparation of *Inf. Gent. Co.*, *Inf. Gent. Co. Conc.* and *Tinct. Gent. Co.*

SERPENTARIA (*Serpent.*), Serpentry rhizome, Not official.

It contains a bitter principle, *aristolochin*, a *volatile oil* and *tannin*.

Dose, $\frac{1}{4}$ to $1\frac{1}{2}$ grains or 0.05 to 0.1 gramme.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

(i) *AQUA AURANTII FLORIS* is the saturated solution of the odoriferous principles of the flowers of *Citrus aurantium*, obtained by distilling fresh flowers with water. It contains a volatile oil, *OLEUM AURANTII FLORIS*, oil of Neroli and a bitter principle.

These are used as *flavouring* for syrups and hair oil.

(ii) *ARISTOLOCHIA*, Indian Birthwort, *Isharmul*, is the dried stem and roots of *Aristolochia indica*. It contains a bitter principle, a volatile oil and tannin.

Tinctura Aristolochiæ (Powder 200, percolated with alcohol 70% 1000). Dose, 30 to 60 min. or 2 to 4 ml.

It is used as a bitter *sialogogue* and *carminative*. In big doses may act as gastro-intestinal irritant.

(iii) **BERBERIS**, *Daruharidra* is the dried roots of *Berberis aristata* contains not less than 1% of berberine and a little tannin, resin, gum and another alkaloid *oxycanthine*. Dose, 30 to 45 gr. or 2 to 3 gramme.

(a) *Berberinæ Sulphas*, $C_{20}H_{19}O_4N(HSO_4)$, obtained from the above is in bright yellow acicular crystals or dark yellow powder with bitter taste. Dose, 1 to 5 gr. or 0.06 to 0.3 gramme.

(b) *Extractum Berberidis*, Rasaut, is the semisolid watery extract, a dark brown or yellow mass. Dose, $\frac{1}{3}$ to 1 gr. or 0.03 to 0.06 gramme.

(c) *Tinctura Berberidis* (Berberis in fine powder 200 and alcohol 60% q.s. to make 0.5% of berberine). Dose, 30 to 60 min. or 2 to 4 ml.

Locally, the extract is a mild astringent. Given *internally*, it is a bitter tonic and is believed to be antiperiodic and one time given in chronic malaria with cinchona alkaloids. Berberine sulphate in 1 to 2% solution (as Orisol, M and B) is infiltrated round the affected areas of *Oriental sore* by means of a fine hypodermic needle once a week.

(iv) **CHIRATA** is the plant *Swertia chirata*, collected when flowering and dried. Dose, 10 to 30 gr. or 0.6 to 2 gramme.

(a) *Infusum Chiratæ Compositum Concentratum* (Chirata 100, dried sweet orange peel 100, lemon peel 200 and alcohol 25%, 1200). Dose, 30 to 60 min. or 2 to 4 ml.

(b) *Tinctura Chiratæ Composita* (Chirata 100, Dried sweet orange peel 37.5, cardamom 12.5 and alcohol 45%, 1000). Dose, 30 to 60 min. or 2 to 4 ml.

Infusum is a popular domestic remedy for general debility with poor appetite and digestion (bitter tonic) especially during convalescence from a severe illness. Tincture may be used in mixtures.

(v) **KALMEGH**, is the dried or fresh entire aerial portion of the plant *Andrographis paniculata*. It contains the bitter principle *andrographolide* 1% and tannin.

Extractum Kalmegh Liquidum (Kalmegh 500, oil of fennel 2, oil of ajowan 2 and alcohol 90% q.s. containing not less than 0.5% of *andrographolide*). Dose, 8 to 15 min. or 0.5 to 1 ml.

Kalmegh is a popular domestic medicine for children with poor appetite and digestion and sluggish liver. The extract may be prescribed as a bitter tonic and laxative along with other tonics.

(vi) **OLEUM NEEM** is the oil expressed from the seeds of *Melia azadirachta*: a deep yellow oil with strongly disagreeable bitter acrid taste,

The oil and its preparations sodium or potassium margosates were one time popular domestic medicines for the treatment of foul sores. These are ingredients of tooth paste also. The leaves of the plant are bitter pot-herb.

(vii) **PICRORHIZA**, *Katuka* or *Katki* is the dried rhizome of *Picrorhiza Kurroa*. The active principles are a glycoside *picrorhizin* and *cathartic acid*. Dose, 10 to 20 gr. or 0.6 to 1.2 gramme. As antiperiodic, 45 to 60 gr. or 3 to 4 gramme.

(a) *Extractum Picrorhizæ Liquidum* (Picrorhiza and alcohol 60% in equal parts). Dose, 15 to 60 min. or 1 to 4 ml.

(b) *Tinctura Picrorhizæ Composita* (Picrorhiza 100, sweet orange peel 37.5, cardamom 12.5 and alcohol 45%, 1000). Dose, 30 to 60 min. or 2 to 4 ml.

Picrorhiza is a useful bitter tonic and appetizer. It has some reputation as antiperiodic in chronic malaria and is combined or alternated with quinine.

(viii) **TINOSPORA**, *Gulanha* is the dried stem with bark intact of *Tinospora cordifolia*. Contains berberine, the bitter principle.

Tinctura Tinosporæ (Tinospora powder 200 and alcohol 60%, to 1000). Dose, 30 to 60 min. or 2 to 4 ml.

Tinospora is a bitter tonic without tannin. It has some reputation as antiperiodic and may be used during convalescence from malaria with iron and quinine.

Pharmacology [and Therapeutics]

There is no common chemical principle in the vegetable bitters and their action is mainly due to their bitter taste. Thus if taken $\frac{1}{2}$ to 1 hour before food, these act as **Sialogogues**: the gastric secretion¹¹⁸ is also increased especially when it is deficient on account of anorexia or prolonged illness and cachexia. This is a reflex act caused by bitter taste acting on the taste buds. An unpleasant taste causes a sharp and powerful reaction on the gustatory apparatus which increases appetite, and flow of gastric juice. This is followed by an increase of **pancreatic secretions**. These especially the aromatic bitters sometimes increase the peristalsis of the stomach and intestine and so act as **carminative**. [These are preferably given in combination with other carminatives and digestants¹¹⁹].

These, however, should not be prescribed when there is any acute inflammatory condition in the stomach or given too long, in which case, these are likely to cause irritation.

In large doses, these produce direct action on the stomach and the gastric secretion is diminished.

Like the volatile oils, these increase the number of **white blood corpuscles** in the peripheral blood.

Infusions of the bitters are frequently injected into the rectum for **thread worm** infection.

Calumba, gentian, chireta and quassia are commonly used. Gentian has a better flavour but cannot be prescribed with iron as the colouring matter is altered. Infusion of gentian with dilute hydrochloric acid has been occasionally given in anorexia of pregnancy.

Quassia is often given by rectal injection for thread worm, 10 to 15 oz. of the infusion being usually required.

Orange peel contains an aromatic oil which is sometimes used for flavouring various substances.

SUMMARY.—Vegetable bitters are **sialogogue** and **stomachic** by reflex action and those with volatile oils are **carminatives** also.

B. DIGESTIVE FERMENTS

Some of the ferments are proteolytic as *pepsin*: some are amylolytic as *diastase* also *malt extract* and others again have more generalised action as *pancreatin* acting on protein and starch also saponifying and hydrolysing fat.

Vegetable ferments as *papain* (from carica papaya) and *bromelin* (from pineapple) are proteolytic.

(118) R

Sod. Bicarb. gr. 15
Tinct. Nuc. Vom. min. 10
Tinct. Zingib. Mit. min. 20
Sp. Chlorof. min. 15
Inf. Gent. Co. ad. fl. oz. 1

One $\frac{1}{2}$ hour before food.

(119) R

Acid. Hydrochlor. Dil. min. 15
Elix. Lactopeptin. min. 30
Tinct. Cardam. Co. min. 20
Inf. Calumb. ad. fl. oz. 1

One $\frac{1}{2}$ hour after food.

PEPSINUM (*Pepsin*)

The enzyme is obtained from the fresh and healthy stomach of pig, sheep or calf. A colourless or light buff-coloured powder or yellow translucent scales, with faintly meaty odour and acid taste : fairly soluble in water and insoluble in alcohol (90%).

It should be stored in a well-closed container in a cool place.

It dissolves in 6 hours in the presence of dilute hydrochloric acid; 2500 times its own weight of coagulated white of an egg.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

PANCREATINUM (*Pancreatin*)

This is a preparation of the pancreas, containing the enzymes, *trypsin* (protein digesting), *lipase* (fat digesting) and *amylase* (carbohydrate digesting). It is colourless or buff-coloured, amorphous powder with meaty odour. It is also prepared by extracting with 25% alcohol the pancreas of goat or calf. It is soluble in water, making a turbid solution, insoluble in alcohol 90% and in solvent ether.

It should be stored in a well-closed container in a cool place.

Dose, 3 to 10 grains or 0.2 to 0.6 gramme.

Pharmacology [and Therapeutics]

PEPSIN.—This has the power of digesting protein into peptone with 0.2% of hydrochloric acid at body temperature and is given with the dilute hydrochloric acid in dyspepsia¹²⁰⁻¹²¹ with deficient gastric secretion and glycerinated pepsin is used for this purpose. In most cases, the deficiency is of the acid and this is indicated more than pepsin. But as lowered acidity tends to diminish the peptic secretion also, a combination of the two is usually prescribed.

[This is especially indicated during convalescence from prolonged illness and in conditions like gastric cancer. This is also useful in chronic diarrhoea and should be given immediately after food and not to be combined with any alkali].

For peptonising purposes, it is inferior to liquor pancreatis.

PANCREATIN.—Either liquor pancreatis or pancreatin in powder form is used for peptonising milk¹²² and less commonly for predigesting meat, about 5 grains of pancreatin being usually

(120) R

Glycer. Pepsin. min. 60
Tinct. Nuc. Vom. min. 10
Sp. Vini Gallici min. 20
Tinct. Cardam. Co. min. 15
Aq. Chlorof. ad. fl. oz. 1

One $\frac{1}{2}$ hour after food, during convalescence.

(121) Take 1 pint of moderately hot milk (of just bearable heat, about 40°C.) and add to it 2 tea-spoonfuls of Liq. Pancreatis and less than $\frac{1}{2}$ tea-spoonful of sod. bicarb. Keep this aside for 15 to 20 min. and then quickly bring it to boiling point. Instead of Liq. Pancreatis, peptonising powder or Benger's food may be used.

Peptonising powder B.P.C. contains pancreatin 20 and sod. bicarb. 80 ; 20 grs. of it will peptonise one pint of milk.

(121) R

Glycer. Pepsin. min. 60
Elixir Lactopeptin. min. 30
Tinct. Cardam. Co. min. 20
Tinct. Opii Camph. min. 20
Aq. Chlorof. ad. fl. oz. 1

One $\frac{1}{2}$ hour after food for chronic indigestion.

sufficient for about a pint of milk. A peptonised food is valuable when the digestion is poor.

An oral administration of pancreatin is of limited value as acid in the stomach greatly destroys it. But food in the stomach continues to be alkaline for some time, the acid being secreted slowly : so if given immediately before or with the meal, it is of some value. It is also given in capsules or as keratin-coated (Enteric coated P. D.) pills which dissolve only in the alkaline juice of the intestine.

Non-official Preparations

GLYCERINUM PEPSINI.—Pepsin 100, hydrochloric acid 11.5, glycerin 600 and water to make 1000 (5½ gr. of pepsin in 60 min.).

Dose, 60 to 120 minims or 4 to 8 ml.

MISTURA BISMUTHI COMPOSITA CUM PEPSINO B.P.C.—Liquor of bismuth 30 min., pepsin 1 gr., tincture of nux vomica 7½ min., dilute hydrocyanic acid 2 min. and chloroform, solution of bordeaux B and water to 60 min.

Dose, 30 to 60 minims or 2 to 4 ml.

LIQUOR PANCREATIS, Pancreatic Solution.—A solution of the extracts of fresh pancreas of pig, prepared by macerating for seven days.

Dose, 60 to 120 min. or 4 to 8 ml.

TRYPSIN, is given to help protein digestion (Dose, 8 to 20 grains) or for peptonising milk.

RENIN, SERIPARIUM.—One grain dissolved in ½ oz. of water will curdle in 1 to 2 hours a pint of fresh milk kept at blood heat. It is obtainable in the form of tablet or essence. Rennet whey and junket are prepared.

PAPAINUM.—The enzyme or mixture of several enzymes obtained by adding alcohol to the freshly drawn juice of pawpaw (*carica papaya*) fruit. This in the form of a powder, in 2 to 10 grs. doses, as the elixir or the glycerinum (Papain 110, dilute hydrochloric acid 80, simple elixir 50 and glycerin to 1000 : Dose, 20 to 60 min. or 2 to 4 ml.) is given in chronic dyspepsia with acidity. It acts both in acid and alkaline media. **IND. PHARM. LIST.**

DIASTASE.—This is the starch digesting ferment obtained from germinating wheat. It should convert 100 times its weight of carbohydrate into sugar and dextrin. *Taka diastase* is prepared by the action of a fungus on wheat bran. This is twice as powerful as diastase. It should be given immediately after food as its activity ceases when gastric acidity exceeds 0.1%. *Diastin* is a similar preparation. Dose, 5 to 8 grains.

LACTO-PEPTINE contains pepsin, pancreatin, diastase, lactase and natural acid from the stomach in the form of powder (Dose, 5 to 10 grs.), tablet or elixir (Dose, 30 to 60 minims) for dyspepsia.

Ptychopapain, *Caripeptic Liquid* and *Diapepsin* are preparations used as digestant, one tea-spoonful after food.

C. PURGATIVES

Any general irritant taken by the mouth is also a gastro-intestinal irritant, causing vomiting and purging. But by *purgatives* or cathartics only those drugs are meant that have a more localised action, more or less limited to the intestine causing evacuations only, without any inconvenient side-issues.

Thus the *therapeutic purgatives* (*Purgare*, to clean) are drugs that are prescribed to hasten evacuation of bowels to get rid of the unnecessary or undesirable contents. These act,

(i) *By increasing the non-absorbable contents of the intestine* : pressure is exerted on the wall of the gut which contracts reflexly. This may be caused by—

(a) Agar agar and other hydrophilic colloids also food containing a large amount of non-absorbable substances especially cellulose.

(b) The collection of fluid in the small and large intestines by slowly absorbable inorganic salts like magnesium sulphate in solution, the fluid so collected not being re-absorbed therefrom.

(ii) *By lubricating the intestinal canal*, passage of intestinal contents are facilitated as by liquid paraffin, many fixed oils as olive oil and mucilaginous vegetables as ispaghul.

(iii) *By irritating the mucous surface* and consequently making it more sensitive to its contents, increasing the local reflex and thus accelerating peristalsis. Vegetable laxatives, castor oil, sulphur, mercurials, anthracenes, phenolphthalein and resinous purgatives act in this way.

(iv) *By direct stimulation of the neuro-muscular mechanism* : This is a systemic action on the intestine along with the same in other places : physostigmine, neostigmine and carbacholum (Doryl) also pilocarpine and apocodeine activate parasympathetic nerve endings and increase the intestinal movements. Posterior pituitary extract acts directly on the intestinal muscles. These are administered hypodermically and therapeutically, neostigmine, acetyl choline, and doryl also posterior pituitary extract are used for intestinal paresis (*hypodermic purgatives*).

Aloes, cascara sagrada, senna (anthracenes), colocynthin and podophyllin (resins) given subcutaneously or intravenously may cause purgation by being excreted into the intestine. But these are not suitable to be administered in this way.

In myxœdema (thyroid deficiency), thyroid extract in adequate dose orally, corrects constipation by activating the metabolic process.

Tetrachlor-phenolphthalein hypodermically (as 0.4 gm. dissolved in oil) acts as a purgative by being excreted into the intestine along with bile and the action is consequently local on the intestine.

It must be understood that many of the purgatives have not a very strict limited action, they may be acting in other parts of the body also.

Drugs of the fourth group with systemic action although often effective in certain types of intestinal paralysis and prescribed for this purpose, are not really purgatives of general use.

USES OF PURGATIVES

(i) Relieve constipation, that is to say, ensure normal evacuation with ease.

- (ii) Expel rapidly from the alimentary canal the undesirable, irritating or toxic substances.
- (iii) Remove a collection of dropsical fluid.
- (iv) Lower the blood pressure and
- (v) Favour elimination of the products of nitrogenous metabolism from the blood when the kidneys are defective.

AN IDEAL PURGATIVE

(a) Should be non-irritating to the stomach causing no vomiting and have a selective action on the intestine only.

(b) Should not cause much gripes and should be fairly certain and not fitful in action : also pleasant to take.

(c) Should not be readily absorbed from the alimentary canal and if partly absorbed, should be readily excreted and not cause much toxic symptoms. (Clark).

After a good purgative action, the colon is well emptied and becomes flaccid. It takes 2 to 3 days to adequately fill it up again and to restore its normal tone to have another evacuation. This after-constipation is often a common event especially with an effective mild oily purgative like castor oil. For the same reason, it is not often essential to ensure *daily* evacuation in a healthy individual by using stronger irritating purgatives. Further, with an irritant purgative like calomel or phenolphthalein, a part of it may be left behind to cause purgation for several days after.

CLASSIFICATION OF PURGATIVES

It is not easy to classify the purgatives. This may be done either according to their chemical properties, the source, or their site, mode and intensity of action. These are obtained either from *mineral* or *vegetable* source with an action of varying intensity from a mild laxative-emollient to a drastic irritant hydrogogue purgative.

SITE OF ACTION.—Castor oil, mercurials and podophyllum act mainly on the small intestine : the anthracenes, phenolphthalein and sulphur on the large and the salines and the drastic purgatives on both small and large intestines.

INTENSITY OF ACTION.—This depends on the special property of the purgative and also the dose. Those having *mild action* are called laxatives, aperients or eccoprotic, causing one or two nearly painless evacuations : these are vegetable laxatives, liquid paraffin, castor oil, salines in small doses and sulphur. Others cause *more complete evacuation* especially of the large intestine, the common site of stagnation : these are anthracenes and phenolphthalein. Others again cause *profuse watery evacuations* : these are concentrated solution of magnesium sulphate and vegetable drastic purgatives.

NATURE OF THE STOOL.—This is often semiformed or soft being the small intestinal contents hurried down: if more liquid, it has abstracted fluid from the mucous membrane as by a saline purgative or has secretions of the intestinal glands also, caused by irritation of a drastic purgative.

CHOLAGOGUE PURGATIVES.—There is no true cholagogue purgative except *bile* and *bile salts*, definitely increasing the biliary secretions. *Histamine* also causes an increased flow of bile. *Calomel* and few vegetable purgatives such as *podophyllum*, *rhubarb*, *jalap* and *scammony* owe this reputation to either hurrying down bile without allowing time for re-absorption or bile activating the purgatives by some solvent action on them.

Warm olive oil, hypertonic solution of magnesium sulphate and fat introduced into the duodenum cause contraction of the gall-bladder and evacuation of bile.

THERAPEUTIC ADMINISTRATION OF PURGATIVES

(i) In the beginning of an acute fever, calomel followed by a mild saline purgative such as Seidlitz powder, occasionally sodium or magnesium sulphate or castor oil is given. Calomel is preferable in acute malaria, hepatic congestion and in biliary stasis: accumulated bile is drained out and vomiting if present is relieved.

(ii) For temporary constipation, castor oil, mercurials, salines, compounds of sulphur and senna, rhubarb or cascara sagrada are prescribed.

(iii) For acute indigestion, food poisoning or bacterial infection of the intestine, small and often repeated doses of calomel, castor oil or salines as milk of magnesia or sodium and magnesium sulphates in combination are given.

(iv) For chronic constipation, a small morning dose of sulphate of magnesia: anthracenes, vegetable laxatives or liquid paraffin usually with agar agar are given at bed time.

(v) Constipation with anæmia and amenorrhœa is often treated with aloes and ferrous sulphate.

(vi) For general anasarca, a concentrated solution of sulphate of magnesia alternating with blue or Guy's pill (in cardiac dropsy) or compound jalap powder or a similar drastic purgative is given. Now effective diuretics are available and accumulated fluid is better drained out by the kidneys.

(vii) For cerebral congestion, high blood pressure or threatened uræmia, strong, rapidly acting purgatives are chosen as sulphate of magnesia, jalap or colocynth.

(viii) For piles and fissure or a painful condition of the rectum, sulphur, compound liquorice powder or liquid paraffin is preferred.

(ix) For post-operative intestinal paresis, hypodermic purgative as neostigmine, carbacholum or posterior pituitary extract is indicated.

(x) Purgatives are to be given with caution in suspected intestinal obstruction, intestinal hæmorrhage, peritonitis, pregnancy, menorrhagia and in severe asthenia also in enteric and eruptive fevers and in kala-azar.

Frequent use of strong cathartics is harmful and not to be encouraged : evacuation should be ensured by regular visit to the closet and use of intestinal lubricants and vitamin B preparations on adequate diet with sufficient fluid and roughages : an active habit is also essential.

MINERAL PURGATIVES

Purgatives obtained from the minerals are *liquid paraffin*, *salines* especially non-absorbable but soluble salts, insoluble *mercurials* and *sulphur*.

(1) LIQUID PARAFFIN.—This acts as a purgative by facilitating an easy passage of intestinal contents. It is frequently prescribed as an emulsion which mixes with the intestinal contents better and not leaks through. (See p. 103).

(2) SALINES.—The commonly used salts are *Sulphates* of *potassium*, *sodium* and *magnesium* : *Magnesium carbonate* and *oxide* : *Sodium phosphate* and to a less extent, *sodium* and *potassium tartrates* and *citrates*.

The intensity of action of these purgatives depends on the relative non-absorbability of the different ions. Therefore magnesium sulphate is most powerful as both the magnesium and the sulphate ions are almost non-absorbable. Those of lesser intensity are magnesium carbonate and oxide, sodium sulphate (also potassium sulphate), sodium phosphate, sodium tartrate and citrate and the feeblest are sodium chloride and bicarbonate. In fact, the last two act as purgative only when 1 to 2 pints of hypertonic solution of these are given per rectum as enema.

Various saline solutions given by mouth to a dog with cæcal fistula showed that sodium chloride in isotonic solution is nearly completely absorbed from the stomach and small intestine : with sodium sulphate, 10 to 20% and with magnesium sulphate, much less are absorbed.

(3) MERCURIALS.—*Metallic mercury* and *subchloride* of mercury act mostly on the small intestine and hurry down the small intestinal contents well mixed with unaltered bile. These to some extent, accelerate the movements of the large intestine also. These have been described under inercury.

(4) SULPHUR.—This forms sulphide which is a mild irritant especially to the large intestine causing soft motions.

Saline Purgatives

1. SODII PHOSPHAS (*Sod. Phosph.*), $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$), Disodium hydrogen phosphate.

Prepared by the action of acid calcium phosphate on sodium carbonate. Occurs in colourless efflorescent crystals, alkaline in reaction and soluble at 15.5° in 7 of water : almost insoluble in alcohol 90% : contains between 99 to 105% of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$.

Dose, 30 to 240 grains or 2 to 16 grammes.

2. SODII PHOSPHAS EXSICCATUS (*Sod. Phosph. Exsicc.*), Na_2HPO_4 .

Prepared by efflorescing sodium phosphate for several days at a moderate temperature in warm air and next drying at 100° , until it ceases to lose weight. This contains not less than 99% of Na_2HPO_4 .

White hygroscopic inodorous powder with saline taste, soluble in 15 parts of water.

Dose, 10 to 75 grains or 0.6 to 5 grammes.

3. SODII SULPHAS (*Sod. Sulph.*), Glauber's salt,
 $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$.

Prepared by the action of sulphuric acid on sodium chloride. Soluble in 3 of water and in glycerin. Transparent, colourless, inodorous, efflorescent crystals with slightly bitter saline taste.

Dose, 30 to 240 grains or 2 to 16 grammes.

4. SODII SULPHAS EXSICCATUS (*Sod. Sulph. Exsicc.*), Exsiccated or anhydrous Sodium Sulphate, Na_2SO_4 .

Prepared by drying sodium sulphate at 100° until it ceases to lose weight, containing not less than 99% of Na_2SO_4 .

A white inodorous hygroscopic powder with a bitter saline taste, soluble in 8 parts of water.

It should be stocked in a well-closed container.

Dose, 15 to 120 grains or 1 to 8 grammes.

5. SODII ET POTASII TARTRAS (*Sod. et Pot. Tart.*), $\text{NaKC}_4\text{H}_4\text{O}_6 \cdot 4\text{HO}_2$, Soda Tartrate, Rochelle Salt.

Prepared by neutralising potash acid tartrate with sodium carbonate : contains between 99 to 104% of $\text{NaKC}_4\text{H}_4\text{O}_6 \cdot 4\text{H}_2\text{O}$. It occurs in colourless crystals or crystalline powder with a cool saline taste : soluble in $1\frac{1}{2}$ of water : insoluble in alcohol 90%.

Dose, 120 to 240 grains or 8 to 16 grammes.

Pulvis Effervescens Compositus (*Pulv. Efferv. Co.*), Seidlitz powder.
See p. 53.

Dose, 192.5 grains. Dissolve the powder in blue paper in 8 fl. oz. of cold water and to it add the powder in white paper and drink while effervescing.

6. POTASSII TARTRAS ACIDUS (*Pot. Tart. Acid.*),
 $\text{KHC}_4\text{H}_4\text{O}_6$, Purified cream of Tartar.

Prepared by the purification of the deposits of wine casks after fermentation of grape juice. Colourless, slightly opaque crystals or gritty white powder with a pleasant acid taste : soluble in 220 parts of cold and in 16 parts of boiling water. The solution is acid to litmus.

Non-official Preparations

CONFECTIO SULPHURIS (*Conf. Sulphur.*), Precipitated sulphur 45, potassium acid tartrate 11, tragacanth 0.5, syrup 21, tincture of orange 5.5 and glycerin 17. Dose, 60 to 120 grains or 4 to 8 grammes.

PULVIS JALAPÆ COMPOSITUS (*Pulv. Jalap. Co.*), Jalap 30, potassium acid tartrate 60 and ginger 10.

Dose, 10 to 60 grains or 0·6 to 4 grammes.

7. **MAGNESII SULPHAS** (*Mag. Sulph.*), Epsom salts,
 $\text{MgSO}_4, 7\text{H}_2\text{O}$.

Prepared by the interaction of native Mag. carb. with Sulphuric acid. Colourless rhombic crystals resembling Zinc Sulphate but moister and with a cool, saline bitter taste. Zinc Sulphate, having nearly the same appearance, has a metallic taste. It is soluble at $15\cdot5^\circ$ in 1·5 parts of water and 1 in 1·1 of glycerin. Contains between 99·5 to 102% of $\text{MgSO}_4, 7\text{H}_2\text{O}$.

Dose, 30 to 240 grains or 2 to 16 grammes.

INCOMPATIBLES.—Alkaline carbonates, sodium tartrate, lime water, phosphoric acid and phosphates, lead acetate and silver nitrate.

OFFICIAL PREPARATIONS.—(i) **Mistura Magnesii Hydroxidi** (*Mist. Mag. Hydrox.*), *Cream of Magnesia*: In 240 min. it contains about 12·5 grains of mag. oxide. See p. 51. Dose, 60 to 240 minims or 4 to 16 ml. (ii) **Mistura Sennæ Composita**, (*Mist. Senn. Co.*), *Black draught*. See p. 51. Dose, 1 to 2 fl. oz. or 30 to 60 ml.

8. **MAGNESII SULPHAS EXSICCATUS** (*Mag. Sulph. Exsicc.*), Dried Epsom salts, MgSO_4 .

Prepared by drying magnesium sulphate at 100° until it has lost approximately 25% of its weight. It contains between 62 to 70% of MgSO_4 .

A white inodorous powder with bitter saline taste: Soluble at $15\cdot5^\circ$ in 2 parts of water, more in hot water.

Dose, 30 to 180 grains or 2 to 12 gramme.

9. **MAGNESII CARBONAS PONDEROSUS** (*Mag. Carb. Pond.*), Heavy magnesium carbonate $(\text{MgCO}_3)_3\text{Mg}(\text{OH})_2\cdot 4\text{H}_2\text{O}$.

Hydrated basic Magnesium carbonate, made by boiling strong watery solution of Magnesium sulphate and Sodium carbonate, evaporating to dryness and washing the product. A white insoluble granular powder.

Dose, 10 to 60 grains or 0·6 to 4 grammes.

Heavy Magnesium carbonate is an ingredient of *Troch. Bism. Co.*

Pulvis Rhei Compositus (*Pulv. Rhei Co.*), *Gregory's Powder*: See p. 53.

Dose, 10 to 60 grains or 0·6 to 4 grammes.

10. **MAGNESII CARBONAS LEVIS** (*Mag. Carb. Lev.*), Light magnesium carbonate, $(\text{MgCO}_3)_3\text{Mg}(\text{OH})_2\cdot 4\text{H}_2\text{O}$.

Hydrated basic magnesium carbonate, made in the above way except that these are mixed cold in dilute solution and then boiled. A very light white inodorous, almost tasteless insoluble powder.

Dose, 10 to 60 grains or 0·6 to 4 grammes.

Used in the preparation of *Pulv. Rhei Co.*

LIQUOR MAGNESII BICARBONATIS (*Liq. Mag. Bicarb.*), *Fluid Magnesia*. See p. 50.

A clear, colourless liquid slightly effervesces on opening a fresh bottle: contains not less than 2·5% of $\text{Mg}(\text{HCO}_3)_2$.

Dose, 1 to 2 fl. oz. or 30 to 60 ml.

11. **MAGNESII OXIDUM PONDEROSUM** (*Mag. Oxid. Pond.*), Heavy magnesia, MgO .

Prepared by heating heavy magnesium carbonate to dull red heat to expel CO_2 . A heavy white inodorous powder is formed, insoluble in water and is slightly alkaline.

Dose, 10 to 60 grains or 0·6 to 4 grammes.

12. **MAGNESII OXIDUM LEVE** (*Mag. Oxid. Lev.*), Light Calcined Magnesia, Light Magnesium Oxide, MgO .

Light magnesium carbonate is heated to dull red heat to expel CO_2 . A light white inodorous powder is formed, almost insoluble in water.

Dose, 10 to 60 grains or 0.6 to 4 grammes.

Used in the preparation of *Mist. Mag. Hydrox.*

13. **MAGNESII TRISILICAS** (*Mag. Trisil.*), Magnesium Trisilicate, $2MgO, 3SiO_2$.

Hydrated Magnesium silicate, prepared by the interaction of solution of magnesium sulphate and sodium silicate. A white, inodorous, slightly hygroscopic powder, insoluble in water. Silicon equivalent should be between 66 to 69.5%; magnesium equivalent is between 30 to 32.5%.

Dose, 5 to 30 grains or 0.3 to 2 grammes.

Pharmacology [and Therapeutics]

The saline purgatives act on the intestine mechanically, by retarding absorption of the fluid and unlike the vegetable purgatives, causing no local irritation and no gripes.

Taken in dilute solution (isotonic* or hypotonic), one or both ions of the salt being more or less non-absorbable, the fluid in which these are dissolved is also not much absorbed. This increases the volume of small intestinal contents, exerts pressure on the intestinal wall and provokes peristaltic reflex. The semi-fluid contents rapidly enter the large intestine, excite this to activity and cause an evacuation often in an hour or two. But if administered in hypertonic solution, these move onwards rather slowly abstracting fluid from the places of contact till become isotonic and the intestine contents only gradually increase in volume taking several hours. The pressure so caused on the intestinal wall starts more active peristalsis, resulting in watery evacuations often several in number. Reaction is more powerful with less absorbable salts.

The salts are mainly excreted in the stools. But if evacuation is not copious and the salts also are to some extent absorbable, these partly get into the circulation and by increasing the non-threshold salt contents and osmotic pressure, cause diuresis. The salts absorbed are excreted in the urine.

If however, purgation is much, on account of fluid loss, the blood gets concentrated, urinary and other glandular secretions are lessened and a sensation of thirst is caused. The body temperature is also slightly lowered. Absorption of food is lessened. Hence the habitual use of saline purgatives for a long time tends to lessen the body weight.

These salts are not purgative when given intravenously. One effect is diuresis: increased blood volume from greater

* Sodium bicarbonate 1.4%, sodium chloride 0.91%, sodium citrate 3%, sodium phosphate 4.46%, sodium sulphate 4%, potassium sulphate 1.12% and magnesium sulphate 6.3% are isotonic.

osmotic pressure and abstraction of fluid from the tissues increases glomerular filtration. The other effect is the specific action of the salts, if there is any.

**SODIUM SULPHATE, SODIUM PHOSPHATE, SODIUM POTASSIUM
TARTRATE, POTASSIUM SULPHATE AND
POTASSIUM ACID TARTRATE**

APPLIED EXTERNALLY, a plain lint soaked in 12% sodium sulphate solution or the desiccated salt with an equal part of glycerin on a **septic wound surface**, has effects like magnesium sulphate glycerin preparations (see p. 210) but less intensive.

TAKEN INTERNALLY, these salt are not readily absorbed and act by local salt action. Thus in concentrated solution, these have an unpleasant bitter **acid taste** (especially sodium sulphate) and cause **nausea** and **vomiting** partly for the taste and partly for abstraction of fluid by salt action from the mouth and stomach.

On the Intestine, these, especially in hypertonic solution, act by abstracting fluid from tissues (salt action) and increasing the intestinal contents which by exerting pressure stimulates peristalsis. The small intestine hurries down its contents into the large intestine which also acts in the same way resulting in evacuation. The first stool may be somewhat solid but soon watery motions start which if many, take the character of bile-stained mucous fluid with very little faecal matter. [These are therefore suitable for draining fluid out of the body in various kinds of dropsy. These are also useful in congestive hepatitis¹²³⁻¹²⁴ acting by abstracting fluid from the portal circulation. Sodium sulphate combined with magnesium sulphate is prescribed in bacillary dysentery¹²⁵ to abstract fluid from the inflamed and oedematous colon]. Sodium phosphate has similar action: it is almost tasteless and is suitable for children: may be given with milk or other food.

Of all these, the sulphate is least diffusible and consequently most powerful. Next comes the phosphate. Tartrates are mostly used in effervescent form: these are partly changed into carbonates, absorbed into the circulation and behave as an alkali salt. Sometimes if the purgative effect is not

(123) R
Sod. Phosph.
Sod. Sulph. aa. gr. 60
Tinct. Rhei Co. min. 30
Inf. Senn. ad. fl. oz. 1

For congestive hepatitis.

(124) R
Sod. Sulph. Exsicc. 22
Pot. Sulph. 1
Sod. Chlorid. 9
Sod. Bicarb. 18

These in grs. in a pint of water, resemble *Carlsbad water*. In granules, *Carlsbad salt* (Effervescent).
DOSE, 30 to 90 grains.

(125) R
Sod. Sulph.
Mag. Sulph. aa. gr. 60
Tinct. Nuc. Vom. min. 5
Syr. Zingib. min. 60
Aq. ad. fl. oz. 1

For acute bacillary dysentery.

very good, a fair amount of the salt is absorbed : the effect is diuresis by salt action on the kidneys¹²⁶.

Potassium tartrate is used in the preparation of Fehling's solution, reagent for the detection of glucose in the urine.

MAGNESIUM SULPHATE

APPLIED EXTERNALLY, it has local salt action on a raw surface in the skin more powerful than other salines [and so it is applied, mixed with glycerin in cellulitis and carbuncle¹²⁷. It relieves pain and by withdrawing fluid by salt action, reduces local tension and helps to control the infection : the slough readily separates out.]

Bi-Mag-Paste in a suitable commercial preparation.

TAKEN INTERNALLY, this is the most powerful saline cathartic. Very little of either of the ions, magnesium and sulphate being absorbable, magnesium sulphate causes powerful salt-action on the bowels. Taken *diluted* with a large volume of water, it quickly increases the bulk of intestinal contents and sets up peristalsis causing rapid evacuations without gripes. So to act rapidly, it should be given in almost isotonic solution (6.5% solution or about 30 grains in one ounce of water) and on empty stomach as food in the stomach retards rapid escape of the gastric contents. If in a *concentrated form*, as in one in two solution, the behaviour is a little different. On entry of a hypertonic salt solution into the duodenum, the pylorus is closed and the fluid passes into the intestine rather slowly. It abstracts fluid from a large part of the alimentary canal, especially from the intestines. This fluid being nearly non-absorbable, slowly increases the volume of the intestinal contents. It thus *takes some time* to act and causes at first semi-solid, afterwards copious and often several, watery stools. Owing to its having a certain amount of local sedative action, it causes less griping and irritation than vegetable cathartics.

Often the action is so rapid (even before the salts reach the colon) that this is probably due to distention of upper portion of the intestine which starts peristalsis in the whole intestinal tract resulting in evacuation.

It has been found that the quantity of fluid passed out in the stool is much larger than what is required to make isotonic solution with the amount of magnesium sulphate taken. So the theory that salts act purely by retarding absorption of fluid from the intestine has been questioned

- (126) R
 Pot. Acid. Tart. gr. 60
 Acid. Citric. gr. 10
 Ol. Limon. min. 2.5
 Sacchar. Solub. gr. 1
 Aq. ad. one pint.
Imperial Drink.

- (127) R
 Mag. Sulph. Exsicc. 9
 Phenol 0.1
 Glycer. 11 (*Morison's Paste*).
 Rub down in a hot mortar.
 To apply in cellulitis.

The explanation probably is that the mechanical stimulus to peristalsis caused by the retained fluid readily excites the colon to empty its normal small intestinal contents in fluid condition, increasing thereby the size of the stool (Clark).

[To ensure a rapid **morning evacuation**, 60 grains of magnesium sulphate in 2 to 4 fluid oz. of lukewarm water on empty stomach in the morning is usually sufficient. This is a suitable purgative for chronic constipation in overweight persons of sedentary habit. Sodium magnesium sulphate effervescent granules¹²³ are more palatable and convenient. In cases of **dropsy** with large collection of fluid in the cellular spaces, a concentrated solution of magnesium sulphate as the saturated solution (about 290 grains per fluid oz.), causes profuse evacuation and removes a large amount of the transudate¹²⁹⁻¹³⁰. To ensure a more complete evacuation a strong vegetable purgative like senna as in "black draught" or compound jalap powder (the cathartic resin with a saline, is also prescribed. But strong hydragogue purgatives for evacuation of fluid are now getting unpopular because these cause asthenia and progressive weakness.

Magnesium sulphate is indicated in persistently **high blood pressure** and obesity. Once a week, at night, a mercurial purgative is given followed by 120 grs. of sulphate of magnesium in the next morning. It is also given in **apoplexy** to relieve the high vascular tension. It is of much value in threatened **uraemia** with raised intracranial pressure. If the patient cannot take it by the mouth, 3 to 4 ounces of it dissolved in about 10 ounces of water are thrown high up into the colon with a soft catheter: a large amount of body fluid with the retained nitrogenous products is abstracted thereby. It was often used in **acute bacillary dysentery**, in the early stages, with considerable tenesmus and much blood and mucus in the stool. With repeated administration, the stool became watery and faecal and the general condition of the patient improved. With the introduction of sulphonamide treatment, the saline purgatives are not now as much used. Mag. Sulph. is however a purgative of choice **after** administration of an **anthelmintic** especially following carbon tetrachloride and tetrachloroethylene treatment.

For the purpose of obtaining the gall-bladder contents, 50 to 100 c.c. of 25% solution of magnesium sulphate is introduced.

(128) R

Mag. Sulph. Exsicc. gr. 385

Acid. Cit. gr. 125

Acid. Tart. gr. 190

Sod. Bicar. gr. 360

Sucros. gr. 105 B.P.C.

Granulate: 1-2 tea-spoonful in a tea-cup of water in morning.

(129) R

Mag. Sulph. gr. 290

Syr. Zingib. min. 120

Aq. Menth. Pip. ad. fl. oz. 1

Mix. A hydragogue purgative.

(130) R

Mag. Sulph. gr. 120

Sp. Menth. Pip. min. 15

Ext. Glycyrrh. Liq. min. 30

Inf. Senn. ad. fl. oz. 1

Taken in the morning following calomel of previous night.

ced into the duodenum with a rubber tube (Einhorn's tube). This causes contractions of the gall-bladder and¹ relaxation of the sphincter of the common bile duct. Therapeutically, Magnesium sulphate given in small and repeated doses by the mouth especially on empty stomach may similarly be helpful in **draining unhealthy bile** out of a diseased gall-bladder and lessening the hepatic congestion.

Only a minute fraction of the magnesium-ion is absorbed and this may reach in the serum about 2 to 3 mg.% and in the cells a little higher. This absorption takes place from the upper bowels, an acid condition of which is favourable for an absorption. The mag.-ion circulates as chloride and carbonate and sulphate combines with sodium salt in the blood to form sodium sulphate slightly reducing thereby the **alkaline reserve**. A part of the sulphate (anion) combines with calcium in the wall of the intestine which tends to **reduce the calcium content** of the blood. A small quantity of sulphide is also formed from the sulphate. The absorbed amount is rapidly excreted by the kidneys causing diuresis and no systemic action of mag.-ion. But given subcutaneously or intravenously, it shows the specific action by **paralysing the sensory portion** of the central nervous system, also to a less extent, the sensory nerve endings without much interfering with the heart or the voluntary muscles. The **motor fibres** are affected after the sensory and the **medulla** last of all, death taking place from respiratory failure. A big dose of magnesium sulphate given orally in concentrated solution to a person with deficient renal function, may occasionally cause comatose condition. [It was used in surgical operations, a 25% solution being injected into the nerve trunk: this caused block anæsthesia like cocaine and of longer duration. It was also sometimes given in tetanus, eclampsia, migraine or angiospasm intramuscularly, intravenously or intrathecally, about 5 c.c. of 25% solution, to relieve the muscular spasm. But, it often fails and is not altogether free from danger: basal anæsthetics as avertin or paraldehyde per rectum and muscular relaxants like curarine are more effective and safer.

Magnesium sulphate is a **chemical antidote** to lead, mercury, arsenic, copper and oxalic acid poisoning.

A large number of food-stuff especially vegetables, contains magnesium and a minute quantity is absorbed therefrom. This ion is necessary for the normal muscle activity, ionic balance and enzyme activation.

Toxic action of the sulphate of magnesium absorbed into the circulation, is counteracted by intravenous injection of 2 to 5 c.c. of 10% calcium chloride solution.

SUMMARY.—The milder saline purgatives as tartrate, phosphate and sulphates of potassium or sodium taken on empty stomach give 1 to 2 soft motions and some diuresis. *Magnesium sulphate* is most powerful and is used in smaller, moderate or bigger doses in diluted or in concentrated form, the former causing more rapid but less watery motions:

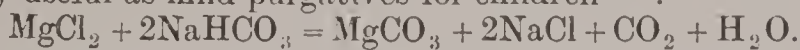
used for ensuring daily evacuation, for lessening hepatic congestion, lowering of blood pressure (for generalised œdema now not so much used), in threatened uræmia, following administration of anthelmintics and in lead poisoning.

MAGNESIUM OXIDE AND CARBONATE

These are insoluble and being antacid are used for reducing the hyperacidity of the stomach in combination with other carbonates [and are often prescribed for all types of hyperacidity especially of gastro-duodenal ulcer].

Magnesium Oxide is the **most effective antacid** and weight for weight, it neutralises more acid than any carbonate, being about 4 times more than sodium bicarbonate, $2\frac{1}{2}$ times more than magnesium or calcium carbonate and 45 times more than bismuth oxycarbonate (Clark). Here, as during neutralisation of the carbonate by the acid, no CO_2 is evolved. It has therefore a very good reputation for the treatment of gastroduodenal ulcer. Heavy carbonate and oxide for their smaller bulk are more suitable for administration as powder and lighter preparations, for mixtures.

These are partly changed into chloride in the stomach, into bicarbonate and hydroxide in the intestine and produce a moderate degree of catharsis¹³¹ by salt action and are especially useful as mild purgatives for children¹³².

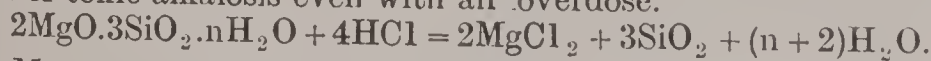


Freshly prepared cream of magnesia is of value in **poisoning** by arsenic (forms an insoluble precipitate) and by mineral acids.

Light magnesium oxide is also used as **dentrifice** to neutralise oral acidity.

MAGNESIUM TRISILICATE

This is a new antacid (Mutch, 1935). Being tasteless, bland and non-irritating, it has no local action. Acid in the stomach makes chloride of magnesium also colloidal silica. This act as effective **acid adsorbent** and mild laxative. The action is slow and sustained continuing for several hours without any risk of toxic alkalosis even with an overdose.



Magnesium chloride reacts with the intestinal contents to form magnesium carbonate which passes out with the faeces and sodium chloride is reabsorbed. Hydrated silicon dioxide formed in the stomach passes into the intestine and acts as the effective acid absorbent : the relief however is not as prompt.

(131) B

Mag. Carb. Lev. gr. 20

Mag. Sulph. gr. 120

Aq. Ment. Pip. ad. fl. oz. 1

One every 2 to 4 hours. (*Mist.*

Alba B.P.C.).

(132) B

Pulv. Rhei Co. gr. 5

Ol. Aneth. min. $\frac{1}{4}$

Sp. Chlorof. min. 15

Mist. Mag. Hydrox. min. 240

1 to 4 tea-spoonful for children.

A gelatinous adherent coating is formed on the ulcer crater and acts locally for a fairly long time although greatest neutralizing action is obtained during the first hour. One gram. of magnesium trisilicate can neutralize about 155 cc. of 0.1/N HCl within four hours. A moderate dose has no action on gastro-intestinal motility but a bigger dose relaxes the bowels from formation of magnesium chloride.

[It is frequently administered in gastroduodenal ulcer. The patient is kept on citrated milk feeds : 30 grs. of magnesium trisilicate is given in the middle of the day and 60 grs. in the morning and at bed time also any time of acidity is complained of. The acid is neutralised, destructive ferments and toxins are removed from the ulcer and a protective coating of hydrated silicon is formed which promote healing].

COMMERCIAL PREPARATIONS are *Gastromag*, *Novasorb* and *Magsorbant*.

SUMMARY.—Magnesium oxide, carbonate and trisilicate are mild laxative and suitable antacids : carbonate is quicker, oxide intermediate and trisilicate slower but more sustained in action and now more frequently used : aluminium hydroxide (p. 141) may be combined : used in gastroduodenal ulcer.

Non-official Preparations

POTASSIUM SULPHATE AND TARTRATE (DOSE, 15 to 60 grains) are used as saline purgatives.

KRUSCHEN SALTS contain in addition to magnesium sulphate, other saline purgatives, a little of sodium chloride and of potassium iodide. DOSE, 1 to 2 tea-spoonfuls in a small tumbler of warm water, taken on empty stomach in the morning.

MAGSIL TABLETS AND GASTROMAG powder are magnesium trisilicate preparations.

CARBOKAOLIN contains carbonates of cal.-mag.-bism. and mag. peroxide with kaolin : acid adsorbent.

BISURATED MAGNESIA, believed to contain bismuth carbonate 8, sodium bicarbonate 40, magnesium carbonate 52. DOSE, $\frac{1}{2}$ tea-spoonful after meals for acidity.

CAL-BIS-MA contains mag. trisilicate, mag. carb., calc. carb., bism. carb. and subgallate, sod. bicarb. and colloidal kaolin (New formula) : this is a useful acid adsorbent and is prescribed in gastro-duodenal ulcer.

DIGENE contains magnesium trisilicate and aluminium hydroxide with sodium chloride, rhubarb, calumba, saccharin and aromatics : one tea-spoonful is prescribed for acidity.

MAGNESIUM PHOSPHATE, (tribasic) in 20 to 60 grains dose every 2nd or 3rd feed, is given for acidity in gastric ulcer.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

(i) MAGMA MAGNESIÆ, MILK OF MAGNESIA.—A milk-like preparation containing about 32 grs. of magnesium hydrate per fl. oz. is given in 1 to 4 ml. doses as antacid and in 8 to 16 ml. doses as laxative.

(ii) TALCUM PURIFICATUM, Creta Gallica Purificata, Purified French chalk, (Mica, *Abhra*), is native magnesium silicate, prepared by boiling with dilute hydrochloric acid and washing the residue : is used in pharmacy or as a dusting powder. Finely pulverised mica is a recognised treatment of hyperacidity in Ayurveda from very ancient times.

II. Sulphur (*Gandhaka*)

(I) SULPHUR SUBLIMATUM, (*Sulphur Sublim.*) Flowers of Sulphur.

It is prepared from crude sulphur or sulphides by sublimation. A fine yellow slightly gritty powder, insoluble in water and alcohol 90%, slightly soluble in oil and fats, completely soluble in carbon disulphide.

Dose, 15 to 60 grains or 1 to 4 grammes.

OFFICIAL PREPARATIONS.—(i) *Pulvis Glycyrrhizæ Compositus* (*Pulv. Glycyrrh. Co.*), Dose, 60 to 120 grains or 4 to 8 grammes. See p. 53.

(ii) *Unguentum Sulphuris* (*Ung. Sulph.*), 1 in 10. See p. 63.

(2) SULPHUR PRÆCIPITATUM (*Sulphur Præcip.*), Milk of Sulphur.

Sulphur is precipitated by hydrochloric acid from a solution prepared by boiling together sulphur and lime with water. A tasteless pale greyish-yellow or pale greenish-yellow powder free from grittiness and from odour of hydrogen sulphide.

Dose, 15 to 60 grains or 1 to 4 grammes.

CONFECTIO SULPHURIS (Not official).—Precipitated sulphur 450, acid potassium tartrate 110, tragacanth 5, syrup 510, tincture of orange 55 and glycerin 170.

Dose, 60 to 120 grains or 4 to 8 grammes.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, although sulphur itself is a bland substance, in contact with protein and alkalies, it is slowly changed into sulphides. These have a mild **irritant** action on the skin. As a certain amount of sulphuretted hydrogen and also pentathionic acid, $H_2S_5O_6$ (which is more likely to be the germicidal agent) are formed, sulphur is very destructive to the animal parasites of **scabies**. It is also useful in other chronic skin diseases as sulphides soften and dissolve the horny epidermis, **keratolysis**. [The ointment is applied on the skin taking care to open out the burrows of the parasites so that the medicine may reach them adequately].

Prolonged irritation by the sulphide may cause a certain amount of inflammation of the skin and therefore it should not be applied continuously too long. It is applied best at bed-time and washed off in the morning.

[Balsam of Peru¹³³ or Beta-naphthol¹³⁴ is sometimes combined with it. In chronic skin affections as psoriasis or seborrhœa, 2% of salicylic acid is combined.

For a similar reason, a sulphur bath, either natural from a hot spring or artificially made, or a lotion is recommended for chronic arthritis and various skin diseases¹³⁵].

(133) R

Bals. Peruv. 1

Ung. Sulph. 7

For scabies.

(134) R

Sulphur. Præcip. gr. 30

Acid. Salicyl.

Hydrarg. Ammon.

Betanaphthol aa. gr. 10

Paraff. Moll. Flav. oz. 1

For scabies and chronic skin diseases.

TAKEN INTERNALLY, it has no action on the stomach but has one of mild irritation on the mucous membrane of the small and more so of large intestine. This is on account of the presence of protein and alkalies in the intestine, sulphur being partly converted into sulphides and sulphuretted hydrogen. So it acts as a mild laxative¹³⁶ causing painless semiformal evacuations. [A favourite preparation is Pulv. Glycyrrhizæ Co. or Confectio Sulphuris frequently prescribed to persons suffering from piles].

One or two c.c. of 1 to 2% suspension in olive oil or colloidal sulphur is sometimes injected intramuscularly every fourth or fifth day, till about 10 injections are given. These cause a reaction and the temperature rises to 103° or more in 6 to 8 hours. Leucocytosis also occurs after each injection. This is sometimes useful in neurosyphilis, chronic joint or skin diseases and in various infective processes.

EXCRETION.—The bulk of the sulphur is excreted with the *fæces*. Ten to forty per cent. of it is absorbed and is excreted partly by the *lung*, giving a special odour to the breath: a little of it through the *skin* but mostly changed into sulphate and an organic compound and is excreted by the *kidneys*. It is a mild diuretic and diaphoretic and is probably of some value in chronic arthritis.

[Sulphur in various forms is sometimes given externally for many skin conditions¹³⁷⁻¹³⁹ and internally as laxative and also for chronic arthritis: some benefit follows from its mild stimulating action].

SULPHUR is often used as ointment or lotion for scabies (*antiparasitic*) and in chronic skin diseases (*keratolytic*). Internally, it is a mild laxative: given parenterally it causes shock fever and at one time used for chronic arthritis, skin diseases and subacute infections but now nearly obsolete.

Non-official Preparations

INTRAMINE, solution No. 1 to be mixed with double the quantity of sol. No. 2 and given intramuscularly in 1 to 4 c.c. doses in syphilis and chronic bacterial diseases.

| | | |
|--|--|--|
| (135) R | Sulphur. Præcip. gr. 15 Zinc. Oxid. gr. 20 Glycer. min. 20 Liq. Calc. Hydrox. min. 180 Aq. ad. fl. oz. 1 (Mackenna). | Alcohol (90%) 12·5 Aq. Rosæ 40 Liq. Calc. Hydrox. ad. 100 (B.P.C.) |
| For scabies and chronic skin diseases. | | (138) R Hydrarg Ammon. Sulphur. Præcip. aa. gr. 30 Ol. Rosmarin. min. 5 Adeps Benz. ad. oz. 1 (Lucas). |
| (136) R | Conf. Sulphur. Conf. Senn. aa. oz. $\frac{1}{2}$ One to two tea-spoonfuls at bed time. | For seborrhœa capitis. |
| (137) R | Sulphur. Præcip. 6·85 Glycer. 3·12 | (139) R Ung. Sulphur. Ung. Zinc. Oxid. Ung. Picis. aa. gr. 120 (Lucas). For chronic eczema. |

CONTRAMINE is given intramuscularly in 0.05 to 0.25 gm. doses for syphilis, chronic gonorrhœa, fibrositis and chronic arthritis.

It is obtained in 1 and 2 c.c. ampoules.

COLLOIDAL SULPHUR.—Made into ointment for external application. 1% sol., is given by the mouth (2 to 4 fl. dr. dose), subcutaneously or intravenously (1 to 2 c.c.).

CALX SULPHURATA, is sometimes prescribed in $\frac{1}{2}$ to 1 gr. doses, repeated every 2 to 3 hours, for boils and other suppurative conditions but is of doubtful value and now replaced by sulphonamides.

POTASSA SULPHURATA, (Liver of sulphur), contains a large quantity of sulphur and is sometimes made into ointment or lotion in various skin diseases¹⁴⁰.

It is also used in the form of a warm bath, one ounce in 3 to 4 gallons of tepid water for chronic joint and muscle pain.

VEGETABLE PURGATIVES

These are *laxatives*, *oils*, *anthracenes* and *resinous* or drastic purgatives. The first group includes some of the residue leaving eatables and are quite popular. The last group for their too powerful action is now not so much used.

(a) LAXATIVES.—These are mostly domestic medicines and sometimes a part of the usual food stuff (*cellulose* roughages) which not being readily absorbed, cause a mild stimulation of the muscular coat of the intestine relaxing the bowels. The others are *tamarind*, *apples*, *figs* and *prunes*: also *agar agar*.

The mucilagenous stuff from *plantago ovata* is an excellent intestinal lubricant and laxative: an emollient laxative (p. 94).

(b) OILS—*Castor oil* and to a less extent, *olive oil* act mostly on the small intestine and are mild purgatives. The former causes mild irritation and the latter is an emollient lubricant.

(c) ANTHRACENE GROUP.—These act mostly on the large intestine, their active principles belonging to anthraquinone group ($C_{14}H_{10}$). These are, *rhubarb*, *senna*, *aloes* and *cascara sagrada*.

There are a few synthetic purgatives also having similar action, the most popular of which is *phenolphthalein*.

(d) DRASTIC GROUP.—These are powerful hydragogue purgatives causing frequent watery evacuations. These act by causing a strong irritation of the mucous membranes and thereby markedly increasing the secretions of both the small and the large intestines.

Some of these as *podophyllin*, *jalap*, *scammony*, also *rhubarb*, *senna* and *aloes*, act better in combination with bile. Probably

(140) B

Zinc. Sulph.

Potass. Sulphur. aa. gr. 60

Aq. ad. fl. oz. 4

(Duhring).

To be used night and morning
for acne and comedones.

like soap, bile makes a colloidal solution with these purgatives and thus delays absorption and brings them in to more intimate contact with the intestinal wall.

(1) AGAR, (*Agar*) Agar-agar, Japanese Isinglass

This is a dried gelatinous substance obtained from sea-weed, *Gelidium Amansii*, *G. cartilagineum* and other allied varieties. Slender, translucent, nearly colourless, lustrous strips, flattened bands, sheets, flakes or coarse powder : insoluble in cold but soluble in boiling water. It consists mainly of *gelose*, an indigestible and unabsorbable carbohydrate and when soaked in water, it swells into a gelatinous mass.

AGAR PULVIS (*Agar Pulv.*) is a greyish white powder used in making pharmaceuticals.

Dose, 60 to 240 grains or 4 to 16 grammes.

One part of Agar boiled with 200 parts of water swells up by imbibing water and forms a jelly which is tasteless. To this are added various flavourings such as milk or fruit juice and made into invalid food but as it is not absorbed, it is of little nutritive value. For the same reason, it increases the volume of the intestinal contents and accelerates peristalsis causing soft bulky stools. So it is combined with paraffin emulsion to make a useful **laxative**. Agar is also used as bacteriological culture medium.

PSYLLIUM SEEDS one tea-spoonful or more taken with a copious drink of water swell up into a gelatinous mass and is a gentle laxative,

(2) OLEUM RICINI (*Ol. Ricin*), CASTOR OIL, *Eranda taila*

This is the fixed oil expressed from the seeds of *Ricinus communis*. The seeds are oval, whitish and with brown or blackish brown spots.

Oil is light yellow in colour, viscid and has a rather unpleasant smell and taste. The active principle is *Ricinoleate of glyceryl*. It has some fixed oils as palmitin and stearin.

The plant grows in all parts of India, especially in Bengal, Bombay and Madras.

Dose, 60 to 240 minims or 4 to 16 ml.

OFFICIAL PREPARATION.—**Acidum Ricinoleicum** (*Acid. Ricinoleic.*) is a mixture of fatty acids obtained by the hydrolysis of castor oil. A yellowish or yellowish brown viscous liquid with a characteristic odour and taste.

Insoluble in water but soluble in alcohol (95%) and in solvent ether.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, it is **soothing** and **sedative** to the skin and mucous membrane and is sometimes dropped into the eye in conjunctivitis [but liquid paraffin is preferred]. One part of the oil in ten of alcohol is a good **hair tonic**.

TAKEN INTERNALLY, in $\frac{1}{2}$ to 1 fluid oz. doses, its chief active principle ricinoleate of glycerol is broken up in the presence of bile by the pancreatic juice into glycerol and ricinoleic acid, an unsaturated hydroxy fatty acid, $C_{17}H_{32}(OH)COOH$, in the duodenum which is irritant and is a prompt purgative, acting in 2 to 6 hours, without much gripes or after-effects.

It is therefore a very popular purgative even for delicate people including young children and pregnant women. It may be prescribed in acute indigestion also: the offending matter is promptly expelled without aggravating the irritation.

A good action effectively empties the colon. It takes 2 or 3 days to fill it up again and restore its tone for the next evacuation. This after-constipation is thus physiological consequence of good action.

Although tasteless, it has a bad nauseating smell [which may be disguised by a few drops of oil of lemon¹⁴¹. It may as well be taken with an aerated water].

It will purge when rubbed into the skin of the softer parts of the body or given per rectum as an enema¹⁴² in cases of intestinal distention.

It is mainly excreted in the faeces: a part of it is absorbed from the small intestine and is oxidised like other fixed oils. It is therefore non-poisonous even in a big dose.

It has no direct action on the large intestine.

RICINOLEIC ACID is used as a solvent for chloroxylenol and is not used as a purgative. Sodium Ricinoleate (*Soricin*) in watery solution is used as a mouth wash in 1 to 4% solution: in combination with alkalis or triethanolamine it makes stable soap and is an **antiseptic** and as it lowers the surface tension, it diffuses into the gum pockets to act on the pus collected.

Soaps formed with triethanolamine (p. 72) is sometimes used as an emulsifying agent in cosmetic creams.

Anthracene Group

The purgative action of the members of this group is due to the presence of various glycosides which yield glucose and an aglucone, a derivative of anthraquinone. Thus *chrysophanol* of rhubarb is dioxymethylanthraquinone: *emodin* of senna is trioxymethylanthraquinone; *rhein* is the oxidation product of emodin: *barbaloin* (glucoside of aloe-emodin) is tetrahydroxymethylanthraquinone, has 3-CH₃ group oxidised into a primary alcoholic group CH₂OH and *d*-arabinose and finally *aloins* are compounds of pentose and hydroxyanthraquinone derivatives. (Dixon.)

(1) ALOE (*Aloe*), Aloes, *Musabbar*.

Aloe is the dry residue obtained by evaporation of the juice coming out of the transversely cut leaves of various species of *Aloe*. Several varieties are in use: Cape, Curacao, Socotrine and Zanzibar aloes. IND. PHARM.

(141) B

Ol. Ricin. min. 120
Mucil. Acac. q.s.
Ol. Limon. min. 2
Aq. Menth. Pip. ad. fl. oz. 1

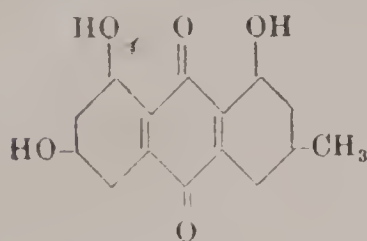
(142) B

Ol. Ricin. fl. oz. 1
Ol. Oliv. fl. oz. 4
Ol. Terebinth. min. 60
Mix. For enema.
For impacted faecal mass.

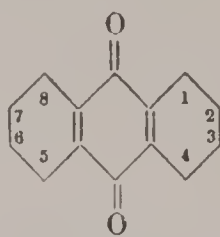
LIST variety is *Aloe barbadensis* or other species of Aloes. It occurs hard masses, yellowish or greenish brown in colour, transparent in their fragments, with a characteristic smell. It is fairly soluble in alcohol 60% and also in water.

Aloe Indica, *Ghrīta Kumari*, as a fresh juice is much used in Indian Medicine. The inspissated juice, popularly called *Musabbar*, was introduced comparatively recently.

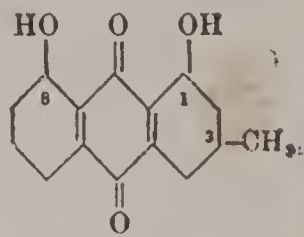
Its active principles are (i) *Aloin* and (ii) *Emodin*. It also contains a little resin, a trace of gallic acid and a volatile oil.



Emodin.



Anthraquinone.



Chrysophanol.

ALOES PULVIS (*Aloe. Pulv.*) is yellowish-brown or reddish brown powdered aloes.

Dose, 2 to 5 grains or 0.12 to 0.3 gramme.

It is an ingredient of *Tinctura Benzoini Composita*, *Pilula Colocynthidis et Hyoscyami* and *Pilula Rhei Composita*.

OFFICIAL PREPARATIONS.—(i) *Pilula Aloes* (*Pil. Aloes*), Dose, 4 to 8 grains or 0.25 to 0.5 gramme. See p. 52. (ii) *Aloinum* (*Aloin.*), Aloin. This is a mixture of the crystalline principles obtained from aloes. This is a pale yellow almost inodorous powder with a very bitter taste. It is soluble in water and alcohol (90%). Dose, $\frac{1}{4}$ to 1 grain or 15 to 60 milligramme.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

(i) *PILULA ALOES ET ASAFŒTIDÆ* (*Pil. Aloes et Asafœt.*).—Aloes, asafœtida, hard soap, each 3 and syrup of glucose 1 or q.s.

Dose, 4 to 8 grains or 0.25 to 0.5 gramme.

(ii) *PILULA ALOES ET FERRI* (*Pil. Aloes et Ferr.*).—Aloes 20, exsiccated ferrous sulphate 10, cinnamon 12, cardamon 12, ginger 12 and syrup of liq. glucose 34 or q.s.

Dose, 4 to 8 grains or 0.25 to 0.5 gramme.

(2) RHEUM (*Rheum*), Rhubarb root.

It is the rhizome of *Rheum Palmatum* and other varieties of *Rheum*. Compact, firm, subcylindrical, barrel-shaped conical or planoconvex pieces usually covered with a bright brownish powder. These have a characteristic aromatic smell and bitter taste. IND. PHARM. LIST variety is *Rheum emodi*, *Rheum webbianum* and other varieties of *Rheum*. The root is obtained from Kashmere, Tibet and China.

The active principles are (i) *Chrysarobin*, (ii) *Chrysophanic acid*, (iii) *Emodin* and (iv) *Rheo-tannic acid*. The former two give the yellow colour. Rheum also contains 35% of calcium oxalate.

RHEI PULVIS (*Rhei Pulv.*), Orange yellow or yellowish brown powder of rhubarb.

Dose, 3 to 15 grains or 0.2 to 1 gramme.

OFFICIAL PREPARATIONS.—(i) *Pilula Rhei Composita* (*Pil. Rhei Co.*), Dose, 4 to 8 grains or 0.25 to 0.5 gramme. See p. 52. (ii) *Pulvis Rhei Compositus* (*Pulv. Rhei Co.*), *Gregory's Powder*: Dose, 10 to 60 grains or 0.25 to 0.5 grammes. See p. 53. (iii) *Tinctura Rhei Composita* (*Tinct. Rhei Co.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 60.

(3) SENNÆ FOLIUM (*Senna Fol.*), Senna leaf, *Sonamukhi*.

Dried leaflets of *Cassia angustifolia* (Tinnevely) or *Cassia acutifolia* (Alexandrian), $\frac{3}{4}$ to $1\frac{1}{2}$ inch long, $\frac{1}{4}$ to $\frac{3}{8}$ inch wide (20 to 50 mm. \times 5 to 16 mm.): lanceolate, greenish yellow in colour, unequal at the base, margins entire sometimes slightly revolute: brittle and with a faint tea-like odour.

This is obtained from two sources and is therefore called Tinnevely Senna and Alexandrian Senna. The active principles are (i) *Cathartic acid*, (ii) *Chrysophanol* and (iii) *Emodin*.

SENNÆ FOLII PULVIS (*Senn. Fol. Pulv.*), green to yellowish green powder of senna leaf.

Dose, 10 to 30 grains or 0.6 to 2 grammes.

Pulvis Glycyrrhizæ Compositus (*Pulv. Glycyrrh. Co.*), Dose, 60 to 120 grains or 4 to 8 grammes. See p. 53.

CONJECTIO SENNÆ (*Conf. Senn.*), Not official: Powdered Senna leaf 10, powdered coriander 4, figs. 16, tamarind and cassia pulp., each 12, prunes 8, extract of liquorice $1\frac{1}{2}$, sugar 40 and distilled water q.s. to 100.

Dose, 60 to 120 grains or 4 to 8 grammes.

SENNÆ FRUCTUS (*Senna. Fruct.*), Senna pod.

This is the dried ripe fruits of *Cassia angustifolia* or *Cassia acutifolia*.

Fruit is pale green with a brown-central area: flat and thin, broadly oblong or subreniform: rounded at the apex, with a small point or scar: cuspidate at the base, sometimes ending in a short stalk: $1\frac{1}{2}$ to 2 inches long about 1 inch wide (4 to 6 cm. \times $2\frac{1}{2}$ cm.). Has about 6 seeds.

OFFICIAL PREPARATIONS.—(i) *Extractum Sennæ Liquidum* (*Ext. Senn. Liq.*), Dose, 10 to 30 minims or 0.6 to 2 ml. See p. 40. (ii) *Infusum Sennæ Concentratum* (*Inf. Senn. Conc.*), Dose, 30 to 120 minims or 2 to 8 ml. See p. 41. (iii) *Infusum Sennæ* (*Inf. Senn.*), Dose, $\frac{1}{2}$ to 2 fl. oz. or 15 to 60 ml. See p. 41. (iv) *Mistura Sennæ Composita* (*Mist. Senn. Co.*), *Black draught*: The concentrated infusion suitably diluted may be used. If crystals separate, these are redissolved by heat. See p. 51. Dose, 1 to 2 fl. oz. or 30 to 60 ml. (v) *Syrupus Sennæ* (*Syr. Senn.*), Dose, 30 to 120 minims or 2 to 8 ml. See p. 55.

(4) CASCARA SAGRADA (*Casc. Sagr.*), Sacred bark, *Rhamni purshiani cortex*.

It is the dried bark of *Rhamnus Purshiana*. Flat pieces, about 4 ins. long and $1/16$ th in. thick (10 cm. \times 2 mm.), purplish brown in colour and the external surface is covered with nearly smooth cork and greyish white lichens (moss). The inner surface is yellow to reddish brown and striated longitudinally. It is obtained from California and collected at least one year before use. It has a characteristic smell and nauseous bitter taste.

Its principle constituent is *emodin* also a little *frangula-emodin*, a glucoside, several resins, acids and a volatile oil.

CASCARÆ SAGRADÆ PULVIS (*Casc. Sagr. Pulv.*).—This is light yellowish brown or olive brown powder.

OFFICIAL PREPARATIONS.—(i) *Extractum Cascaræ Sagradæ Siccum* (*Ext. Casc. Sagr. Sicc.*), This is passed through a fine No. 22 sieve. Dose, 2 to 8 grains or 0.12 to 0.5 gramme. See p. 39. (ii) *Extractum Cascaræ Sagradæ Liquidum* (*Ext. Casc. Sagr. Liq.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 39. (iii) *Elixir Cascaræ Sagradæ* (*Elix. Casc. Sagr.*), Dose, 30 to 60 minims or 2 to 4 ml. See p. 38.

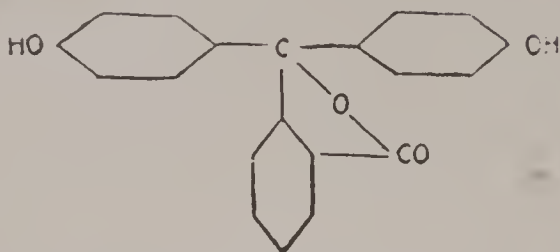
(5) PHENOLPHTHALEINUM (*Phenolphthal.*), Phenolphthalein, *Purgen*, $C_{20}H_{14}O_4$.

This is a synthetic preparation, made by heating phenol with phthalic anhydride and sulphuric acid and subsequent purification.

It is a colourless or slightly yellow crystalline or amorphous powder, inodorous and tasteless, almost insoluble in water, soluble in alcohol 95%.

It makes a red solution with alkali hydroxides which becomes colourless on adding dilute acids.

Dose, 1 to 5 grains or 60 to 300 mg.



Tabellæ Phenolphthaleini (*Tab. Phenolphthal.*).—Each tablet, if not otherwise stated contains 2 grains. Dose, as of the above. See p. 58.

Pharmacology [and Therapeutics]

The four purgatives of this group, Rhubarb, Senna, Aloes and Cascara, with active principles more or less related to one another, being of the anthracene group ($C_{14}H_{10}$), all containing emodin or trioxymethylantraquinone, $C_{14}H_4(CH_3)(OH)_3O_2$ and some, chrysophanol or dioxymethylantraquinone, $C_{14}H_5(CH_3)(OH)_2O_2$ in addition, act as irritant to the large intestine. As these active principles are slowly liberated from the crude drug, these do not act until they reach the colon. So these are called **colonic purgatives** and take a fairly long time to act : about 10 to 12 hours. But these principles themselves are not so suitable in the pure state because these are likely to be partly absorbed before reaching large intestine and cause toxic symptoms rather than free purgation, especially irritation of the kidneys during excretion. A part of it may appear in the milk of a nursing mother and relax the bowels of the infant.

The main advantage is that they do not increase the peristalsis of the stomach or the small intestine, but only of the large intestine, the sluggish action of which is mostly responsible for chronic constipation. These are fairly certain in their action and cause a moderate amount of nearly painless purgation. These do not require bile for their action except probably rhubarb. On account of bitter taste these are usually prescribed in the form of pills.

These cause some congestion of the pelvic organs also and therefore increase the **menstrual flow** and in pregnancy may cause abortion.

Aloes—

It is **bitter** and therefore acts as **stomachic**. Aloin is a glycoside which on hydrolysis slowly liberates an anthraquinone derivative. Its action as a **purgative** is favoured by alkalies and perhaps also by bile but causes gripes. [It is usually

prescribed in pill form combined with a volatile oil and hyoscyamus¹⁴³]. But as it causes rectal congestion, its habitual use may cause piles.

It causes slight pelvic congestion also and is an **emmenagogue**. [It is usually given in pill form combined with iron to anæmic women with scanty menstruation¹⁴⁴].

Aloin, given intravenously to a rabbit, causes little purgation but much renal irritation and powerful contraction of the uterus. In a human being, however it does not cause as much renal irritation but to use as a purgative, aloes itself is preferable. It is an unsuitable purgative for pregnant women and in people suffering from piles. A part of it excreted in the milk of the nursing mother, may relax the bowels of the suckling.

Rhubarb—

It is **bitter** and in small doses slightly **stomachic**¹⁴⁵. In bigger doses, it is a **purgative** with doubtful cholagogue action and probably requires the presence of bile for its activity¹⁴⁶. This is the only anthracene purgative to contain tannic acid which causes **after constipation** and so is unsuitable in habitual constipation. Its purgative action is mild and is commonly given to children¹⁴⁷⁻¹⁴⁸. It contains chrysophanol which stains the acid urine yellow and to a less extent stains the skin and milk. [It is a useful purgative for indigestion caused by unsuitable or indigestible food but castor oil is better]. It causes **gripes** and prescribed along with other purgatives and carminatives. Given to the nursing mother, it may relax the bowels of the suckling as it is excreted in the milk. Occasionally it causes headache and nausea and rarely skin eruptions.

- (143) ℞
Phenolphthal. gr. 1 to 2
Aloe gr. 1 to 2
Ext. Nuc. Vom. gr. $\frac{1}{4}$
Capsicum gr. $\frac{1}{2}$
Ext. Hyoscy. Sicc. gr. 1
A good dinner pill.

- (144) ℞
Ferr. Sulph. Exsicc. gr. $1\frac{1}{2}$
Aloe gr. 1
Ext. Nuc. Vom. gr. $\frac{1}{4}$
Ext. Hyoscy. Sicc. gr. $\frac{1}{2}$
Sap. Dur. gr. $\frac{1}{4}$
Syr. Glucos. Liq. q.s.
Pil. One 2 to 3 times daily.

- (145) ℞
Sod. Bicarb. gr. 15
Tinct. Rhei Co. min. 25
Tinct. Zingib. Mit. min. 20
Sp. Ammon. Aromat. min. 15
Aq. Chlorof. ad. fl. oz. 1
One $\frac{1}{2}$ hour before food.

- (146) ℞
Hydrarg. Subchlor. gr. 2
Pil. Rhei Co. gr. 3
Pil. To be taken at bed-time.

- (147) ℞
Mag. Carb. Pond. gr. 15
Pulv. Rhei Co. gr. 10
Sp. Ammon. Aromat. min. 15
Ol. Anis. min. 1
Aq. ad. fl. oz. 1
Red Mixture.
One tea-spoonful every 3-4 hours

- (148) ℞
Tinct. Rhei Co. min. 24
Ext. Senn. Liq. min. 48
Elix. Casc. Sagr. min. 24
Ficorum (Fig) gr. 140
Sucros. gr. 240
Aq. ad. fl. oz. 1
Comp. Syr. of Figs.
One tea-spoonful at bed-time.

Senna—

This is also a popular purgative and is often given as infusion of the pods; six to ten of these are soaked overnight in cold water and given in the next morning. In addition to emodin, this, like rhubarb, contains chrysophanol which makes the urine yellow. It causes more griping than other members of the group. [Therefore this should be given with carminatives like cinnamon or ginger¹⁴⁹]. It is sometimes combined with saline purgatives to ensure a more complete evacuation of the bowels, as in "black draught". Confection of senna and compound liquorice powder are mild purgatives and prescribed in piles to ensure a relaxed motion.

Cascara Sagrada—

Given in small doses as 10 to 15 minims of the liquid extract, it acts as bitter stomachic. In 30 to 60 minims doses of the liquid extract it acts as a purgative: it is the mildest of the anthracene group. It has a tonic action on the gastrointestinal tract and is a good purgative for habitual constipation. A progressively increasing dose is not required to be effective. It relaxes the bowels with very little gripes which makes it so popular¹⁵⁰. It is often combined with other purgatives to make pills and is best given at bed-time to act in the following morning.

Phenolphthalein ($C_{20}H_{14}O_4$)—

This, a synthetic purgative, is described here on account of the similarity of action. It is bland, inodorous and tasteless which make it an agreeable purgative. Being insoluble in water, it is prescribed as an emulsion with liquid paraffin or made into pills. Taken internally, it passes through the stomach unchanged. It is dissolved in the intestine by bile and alkali when it causes mild irritation of the small and more so of the large intestines relaxing the bowels without much gripes¹⁵¹. It is often mixed with paraffin agar emulsion which causes painless evacuation. It usually takes 4 to 7 hours to act.

It is mainly excreted with the faeces unchanged but a small quantity is absorbed and excreted in the urine. As it turns

(149) R

Mag. Sulph. gr. 50

Sp. Cinnam. min. 10

Syr. Zingib. min. 60

Inf. Senn. ad. fl. oz. 1

One every 2 hours till the bowels move.

(150) R

Sod. Bicarb. gr. 10

Tinct. Nuc. Vom. min. 10

Ext. Casc. Sagr. Liq. min. 20

Sp. Chlorof. min. 15

Inf. Gent. Co. ad. fl. oz. 1

One hour before food, as a stomachic and laxative,

(151) R

Ext. Casc. Sagr. Sicc.

Phenolphthal.

Aloe aa. gr. 1

Capsicum gr. $\frac{1}{2}$

Ext. Nuc. Vom. Sicc.

Ext. Bellad. Sicc. aa. gr. $\frac{1}{2}$

Ext. Gent. q.s. Dinner pill.

pink in alkaline solution, if the urine happens to be alkaline. it takes red colour.

Phenolphthalein was long used by the chemists as pH indicator.

A part of it is also excreted in the bile which being absorbed, comes back to the bowels. Therefore the purgative action tends to persist for a few days till the drug is slowly passed out of the system. If administered frequently, has **cumulative** effect causing in a few days excessive purgation. For the same reason, it acts as a purgative when injected subcutaneously.

It sometimes causes macular or urticarial eruptions on the skin and less commonly on the mucous membrane. These may be persistent and even relapsing.

Given in big doses, during excretion it causes renal irritation.

Non-official Preparations

PURGATIN (DOSE, 10 to 15 grs.), EXODIN (DOSE, 15 grs.) and APERITOL (DOSE, 3 grs.) are other synthetic purgatives of the group but less popular.

3. Drastic Purgatives

(1) *IPOMŒA* (*Ipom.*), Orizaba Jalap, Scammony root. It contains not less than 12% of resin.

This is the dried root of *Ipomœa orizabensis*. Irregular, tough, fibrous pieces (size, 3 to 10 cm. x 0.5 to 4 cm.), externally greyish black and wrinkled, internally greyish or brownish sometimes resinous; faint odour and slightly acid taste.

IPOMŒE PULVIS (*Ipom. Pulv.*) is light grey or greyish brown powdered ipomœa.

IPOMŒE RESINA (*Ipom. Res.*).—This is the mixture of resins obtained from *Ipomœa*, extracted with alcohol 90%.

Brownish translucent, brittle pieces breaking with a resinous fracture or a pale brown powder: agreeable fragrance and acid taste. Insoluble in water but soluble in alcohol (90%) and solvent ether.

DOSE, $\frac{1}{2}$ to 3 grains or 30 to 200 mg.

It is an ingredient of *Ext. Colocynth. Co.* and *Pil. Colocynth. et Hyoscy.*

PULVIS JALAPÆ COMPOSITUS (*Pulv. Jalap. Co.*), Not official.—Jalap 3, potassium acid tartrate 6 and ginger 1.

DOSE, 10 to 60 grains or 0.6 to 4 grammes.

(2) *COLOCYNTHIS* (*Colocynth.*), Colocynth pulp, Bitter calumba, *Indravavuni*, *Makal phal*.

Light, whitish or pale yellow spongy ball, convex with ridges, the fruit of *Citrullus Colocynthis*, size, 6 cm. x 2 cm., in the pulp of which the seeds are embedded. The active principle is a glucoside, *colocynthin*. It also contains some resins, gum and mucilage.

It is obtained from Sinyrna, France, Spain and Trieste. The Indian variety grows all over the plains of drier parts of India.

COLOCYNTHIDIS PULVIS (*Colocynth. Pulv.*) is yellowish white powdered colocynth.

OFFICIAL PREPARATIONS.—(i) *Extractum Colocynthidis Compositum* (*Ext. Colocynth. Co.*), DOSE, 2 to 8 grains or 0.12 to 0.5 gramme. See p. 39.
(ii) *Pilula Colocynthidis et Hyoscyami* (*Pil. Colocynth. et Hyoscy.*), DOSE, 4 to 8 grains or 0.25 to 0.5 gramme. See p. 52.

(3) *PODOPHYLLUM (Podoph.)*, *Podophyllum Rhizome*.

Dried rhizome and roots of *Podophyllum peltatum* of North America, subcylindrical, smooth or slightly wrinkled pieces, with enlargement at intervals of 5 to 30 cm. : enlargements are about 1 to 2 cm. \times 1.5 cm. and cylindrical parts, about 5 mm. thick : brittle rootlets or their scars. Have a characteristic faintly narcotic smell and bitter taste. Resin content is not less than 4%,

Its active principles are (i) the resin which is the purgative and is official and (ii) an alkaloid, berberine. The former contains two isomeric principles, *podophyllotoxin* and *picropodophyllin*.

PODOPHYLLI PULVIS (Podoph. Pulv.) is a light brown powder.

Dose, 2 to 10 grains or 0.12 to 0.6 gramme.

PODOPHYLLI RESINA (Podoph. Res.), *Podophyllin*.

The active purgative principle is a crystalline body, *podophyllotoxin*.

It is an amorphous, light brown, orange-brown or greenish yellow powder, obtained by percolating the root and then precipitating the resin with water.

Insoluble in water, partially soluble in hot water but freely soluble in alcohol 90%.

Dose, $\frac{1}{4}$ to 1 grain or 15 to 60 mg.

PODOPHYLLUM INDICUM (Podoph. Ind.), *Indian Podophyllum*.

Podophyllum hexandrum grows in the Himalayas from Sikkim to Hazara and also in Simla, Garhwal and Kashmere. The supply is mostly obtained from Kashmere and Hazara. Contains not less than 8% of resin.

The resin is official and may be used as a substitute for *podophyllum* resin, the action being the same.

PODOPHYLLI INDICI PULVIS (Podoph. Ind. Pulv.) is a light brown powder.

Dose, 2 to 10 grains or 0.12 to 0.6 gramme.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, these are powerful irritants but are not used as such.

Taken INTERNALLY, their main action is due to the powerful glucosides. These are much more powerful than any other group of purgatives and by their irritant action on the intestinal glands, a copious secretion is poured into the intestine, causing profuse, watery stools. In about 3 hours, the small intestinal contents are emptied which quickly run out of the large intestine without much cæcal control. These are therefore called **drastic** and **hydragogue purgatives**. Usually the glucosides pass so quickly that there is no damage to the intestinal epithelium but sometimes, especially if given in bigger doses, the irritation is so profound that it may extend into the stomach, causing **nausea** and **vomiting** and the intestinal secretion may take up mucopurulent or even hæmorrhagic character, containing shreds of desquamated epithelia. These may even cause irritation of the kidneys and the bladder, causing **painful micturition**.

These are administered in cruder state, the active principles being liberated in the intestine. These in purer form are **gastric irritants** and incapable of therapeutic administration.

In spite of their powerful action these, in therapeutic doses do not cause as much gripes as the anthracenes probably because of more fluid condition of the contents, the faecal matter runs out of the intestine with greater ease.

The presence of **bile in the intestine** increases the activity of almost all of these purgatives.

Given subcutaneously or intravenously, podophyllotoxin and colocynthin are excreted into the bowels and the kidneys, causing frequent purgation and also nephritis.

Drastic purgatives are now not very much used for any purpose: the elimination of the intestinal contents or accumulated fluid may be done by other more convenient and harmless methods such as by milder purgatives or diuretics.

Scammony Resin—

It has the usual action of the group. In addition to being a powerful **hydragogue purgative**, it is an **anthelmintic**¹⁵² in combination with santonin for expelling round worms. But on account of its griping action, it is not very popular.

Jalap Resin—

It causes active intestinal peristalsis and profuse **watery evacuations**. As it is less **griping**, it is more popular and was frequently given in a generalised œdematous condition (anasarca), especially of chronic kidney diseases. The compound powder is frequently prescribed: the saline purgative in it is a helpful synergist: this by liquefying the stool makes the evacuation easy without gripes.

Jalap is sometimes made into pills with other purgatives in obstinate constipation¹⁵³⁻¹⁵⁴.

Colocynth Pulp—

It contains a **bitter** amorphous glucoside, but is seldom used for this property as a **stomachic**. It is a powerful **hydragogue purgative**¹⁵⁵ causing profuse intestinal secretion but it is very irritant and is **likely to cause gripes**. Therefore

(152) R
Santonin. gr. 1
Scammon. Res. gr. $\frac{1}{4}$
Hydrarg. Subchlor. gr. $\frac{1}{2}$
At bed-time for a child of 4 to 5 years.

(153) R
Aloin
Jalapin
Gingerin aa. gr. $\frac{1}{2}$
Glycer. Trag. q.s. (Samaritan).
Pil. One at bed-time.

(154) R
Jalap. Pulverat. gr. 2
Colocynth. gr. $1\frac{1}{2}$
Zingiber gr. $\frac{1}{4}$
Ol. Caryoph. min. $\frac{1}{4}$
Syr. Glucos. Liq. q.s.
Pil. 1 to 2 at bed-time.

(155) R
Ext. Colocynth. Co. gr. 3
Pil. Hydrarg. gr. $\frac{1}{2}$
Ext. Hyoscy. Sicc. gr. 1
Capsicum gr. $\frac{1}{4}$ (Lucus).
Pil. One or two at bed-time.

it is combined with other purgatives and also with hyoseyamus and carminatives.

Podophyllum—

Podophyllum is a **local irritant** and in 20% solution in liquid paraffin, it is sometimes applied on granuloma inguinale and condylomata.

This contains a **cathartic** resin acting more powerfully on the small intestine especially on duodenum.

It is comparatively slow in action and takes about 10 to 12 hours to act : like calomel, it hurries down bile and deeply bile-stained liquid motions are passed with considerable **gripes**. It is thus only an **indirect cholagogue**¹⁵⁶⁻¹⁵⁷.

In small doses, it is of value in torpid liver of chronic congestion.

Podophyllotoxin, injected subcutaneously, causes purgation and also renal irritation and if the dose is big enough, hæmorrhage into various organs.

Non-official Preparations

CROTON OIL (*Jaipal*),—It contains a resin, glyceryl of crotonoleic acid, believed to be the purgative principle. It is a powerful irritant and a very strong purgative and causes gripes. One or two drops of it with sugar or butter are occasionally given. Its small bulk makes it suitable for an unconscious or insane patient. But an enema is more preferable.

ELATERINUM in 1/40 to 1/10 grain dose was formerly much used as hydragogue purgative.

KALADANA (*Nilkalmi*), **TURPETH** (*Tribrit*, *Teori*), also *Pulvis Kaladana Compositus* and *Pulvis Turpethi Compositus* (kaladana or turpeth 700 g., pot. acid. tart. 700 g. and ginger 100 g., all finely powdered).

DOSE, 60 to 90 grain or 4 to 6 gramme : **IND. PHARM. LIST.**

These contain powerful resins with action similar to jalap and are prescribed in generalised œdematous condition as hydragogue purgatives.

EUONYMIN, IRIDIN AND LEPTANDRIN : These are less powerful than the above and do not cause as much catharsis or gripes. In small doses as 1 to 2 grains, these are bitter stomachics and are often combined with other purgatives into pills and frequently given for constipation associated with chronic congestion of the liver¹⁵⁸.

13. DRUGS USED AS VEHICLE

This group includes *oil of theobroma* (used in suppositories), *pyroxylin* (makes collodion) and *gelatin* (makes throat pastilles and eye discs).

- (156) B
Podoph. Res. gr. $\frac{1}{2}$
Aloe gr. $\frac{1}{4}$
Ext. Gent. q.s.
Resembles *Carter's little liver pill*. (Cholagogue purgative).
(157) B
Podoph. Res. gr. $\frac{1}{4}$
Aloin gr. $\frac{1}{4}$
Jalap Pulverat. gr. $\frac{1}{4}$
Ol. Menth. Pip. min. $\frac{1}{2}$

- Glycer. Trag. q.s.
Resembles *Doan's back-ache pills*.
(Cholagogue purgative).
(158) B
Euonymin
Leptandrin
Aloe aa. gr. $\frac{1}{4}$
Ext. Nuc. Vom. gr. $\frac{1}{4}$
Ext. Hyosey. Sicc. gr. $\frac{1}{4}$
Glyc. Trag. q.s.
A dinner pill, taken at bed-time.

ACETONUM, Acetone, $C_3H_6O_3$, Not official, is a colourless, transparent volatile liquid with a characteristic odour and sweetish pungent taste.

It is miscible with water, alcohol, ether, oils and is a solvent for fats, resins, pyroxylin, celluloid and many other organic substances.

OLEUM THEOBROMATIS (*Ol. Theobrom.*), Cocoa butter, Cocoa butter

A solid fat expressed from the roasted seeds of *Theobroma cacao*, obtained from Demerara and Mexico. It is yellowish in colour and melts at 30° to $35^\circ C$. Its chief constituents are *stearin*, a little of *olein* and an alkaloid, *theobromine*.

Shelled seeds (cocoa nibs) have the *oil*, which pressed out and the residue powdered, is called *cocoa*. The nibs made into paste with sugar and vanilla is *chocolate*.

Pharmacology [and Therapeutics]

As oil of theobroma melts at body temperature, it is used for making all suppositories except that of glycerin and in tropical countries requires the addition of a certain amount of beeswax to give it sufficient solidity.

PYROXYLINUM, Pyroxylin

Pyroxylin is nitrated cellulose: prepared by immersing cotton wool (fat free) in a mixture of sulphuric and nitric acids and then it is drained and dried. It is soluble in a mixture of solvent ether 3 and alcohol 90%, 1 and is highly inflammable.

COLLODIUM FLEXILE, COLLODION. Pyroxylin 2%. See p. 37. Alcohol 90% may be replaced by Industrial Methylated Spirit.

Pharmacology [and Therapeutics]

Applied to the skin, alcohol and solvent ether evaporate, leaving a thin coating on the place and this acts as a **protective** to any superficial small wound such as the puncture spot of an injection or a small fresh abrasion. As the cellulose film slightly contracts, collodion is helpful in approximating the two wound margins nearby. Salicylic acid dissolved in collodion is used as **corn solvent**.

GELATINUM (*Gelat.*), Gelatin

Prepared by the action of boiling water (partial hydrolysis) on animal tissues (collagen) as from skin, tendons, ligaments and bones and evaporating the aqueous extract to dryness.

It consists of colourless or pale yellow translucent sheets or shreds with very little odour or taste. It is insoluble in cold (which slowly absorb 5 to 10 times its own weight of water) but soluble in hot water. The watery solution is precipitated by tannin. It is a constituent of Glycerin suppository and all lamellæ.

GELATINUM ZINCI (*Gelat. Zinc.*), *Unna's paste*. See p. 40.

Pharmacology [and Therapeutics]

For its physical properties, gelatin is frequently used as a **basis** for throat pastilles, eye-discs, bougies, pessaries and also as capsules for unpalatable drugs and is a useful pill-coating.

It is also used in making jellies and has some **food value**.

It is believed to be **hæmostatic** : probably, it acts on account of its high calcium content [and is applied locally as *gelatin sponge* available in sterile glass tubes and it is not now-a-days so often given by the mouth, subcutaneously or intravenously for this purpose.

A 6% gelatin solution, available as ready made sterile solution, 500 to 1000 ml. intravenously is sometimes used for the treatment of shock where blood plasma is not available.

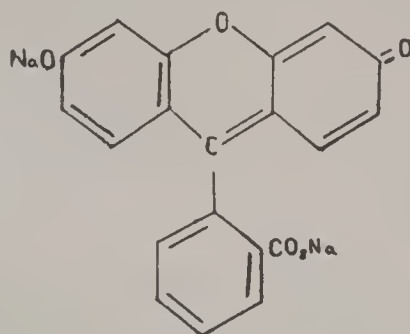
It contains about 25% of *glycine* and 80 grms. of it made into jelly by boiling may be given orally daily, as a substitute for glycine itself in *Myasthenia gravis*.

14. DRUGS USED FOR DIAGNOSTIC TESTS

This group includes *fluorescein* (for detecting a corneal ulcer) ; for skiagraphy, *barium sulphate* (for alimentary canal) : *iodophthalein* (for cholecystography) : *iodoxyl* and *diodone* (for pyelography) and *methylene blue* and *indigo-carmin* (for kidney efficiency test).

FLUORESCEINUM SODIUM (*Fluoresc. Sod.*), Soluble Fluorescein, $C_{20}H_{10}O_5Na_2$

It is the Di-sodium salt of fluorescein, (tetra-oxyphthalophenon anhydride), prepared by the condensation of resorcinol and phthalic anhydride. It is an orange red powder, hygroscopic with no smell or taste and is soluble at 15.5° in 1 of water causing fluorescence and 1 in 5 of alcohol (90%). It must be kept in a well closed container.



Pharmacology [and Therapeutics]

A 2% solution is dropped into the eye for detecting corneal ulcers. Only the injured portion takes a green stain.

Sodium fluorescein in 5% solution with sodium bicarbonate in 5% solution, 0.7 c.c. per 10 lbs. of bodyweight is rapidly

injected into the antecubital vein : the patient is examined in a darkened room : a brilliant green fluorescence is seen on the lips with long wave ultra-violet lamp : the time taken for this colour to appear calculated from the time of injection, indicates the circulation time.

Inoperable cancer cases were treated by giving intervenous injections of it in 2 to 2½% solution and also applied locally, followed by a dose of the X-rays of suitable penetrating power. Although some benefit was claimed, the results have not been largely confirmed.

BARIUM SULPHAS (*Barii Sulphas*), Barium Sulphate, BaSO₄

It is prepared by the interaction of a soluble barium salt and a soluble sulphate. It is a white, tasteless, heavy, amorphous fine powder insoluble in water, very slightly soluble in acids.

Pharmacology [and Therapeutics]

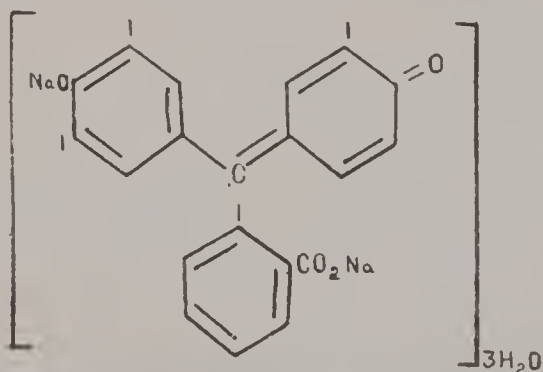
Barium Sulphate is a bland non-absorbable powder which passes through the alimentary canal unchanged. It is **opaque to the X-rays** : 4 oz. of it, made into a meal with gruel and milk, is given by the mouth or rectum and the skiagrams show the contour of the alimentary canal. Care should be taken not to mistake it for Barium sulphide which is poisonous.

The barium-ion has specific action on all forms of muscles, striped, unstriped and cardiac, increasing the contractility and diminishing the relaxation, whether applied direct or reaching through the circulation. Thus *Barium Chloride*, taken by the mouth, causes nausea, vomiting and diarrhoea associated with colicky pain from its effect on the muscles of the stomach and intestine. The heart becomes slow and more forcible and the bronchioles are constricted. Ultimately death follows from the paralysis of the central nervous system.

It is given in ½ gr. doses 3 times daily, cautiously increased, in complete heart block, sometimes with benefit.

Barium sulphide (Not official) 5, powdered soap 1, French chalk 7 and starch 7 made into a paste in 3 parts of water, applied to the skin for 5 minutes as a **depilatory**.

IODOPHTHALEINUM (*Iodophthal.*), C₂₀H₈O₄I₄Na₂·3H₂O Disodium tetra-iodophenolphthalein : Stipp



It is prepared by the iodination of phenolphthalein, containing not less than 87% of dry phthalein and 61 to 63% of iodine. It is a blue or

violet blue inodorous crystalline powder with an astringent saline taste. It is soluble at 15.5° in 7 parts of water and slightly in alcohol 90%.

Dose, $\frac{1}{2}$ to $\frac{1}{2}$ grain per pound or 40 to 60 mg. per kilo body weight, up to 75 grains or 5 grammes orally.

Pharmacology [and Therapeutics]

The dye is **opaque to the X-rays** and is used as a contrast medium. Given by the mouth it is absorbed, carried to the liver and excreted with the bile. If the bile capillaries are permeable, the common bile and the cystic ducts are patent, it is excreted into the gall-bladder whose shadow is seen under the X-rays.

[The patient is prepared by giving a dose of purgative and a powder containing taka-diastase and thymol to lessen gas formation in the intestine, 24 hours earlier].

He takes a light supper containing no fat, usually toast and skimmed milk; only plain water or water with bicarbonate of sodium is drunk freely afterwards. This is required to adequately wash down the dye.



Fig. 6.—The gall-bladder is visualised by cholecystography with Iodophthalcin

The dye, as in the form of Opacol, Stipolac or T.I.P., is obtained as a powder in sealed phials. Each containing 4 grammes is stirred up in half tumbler of water and immediately taken by the mouth in a single dose at bed time. This is followed by copious drinks of water. The skiagrams of the liver are taken 14 and 16 hours after: on the next day one hour after the second film, a fatty meal consisting of buttered eggs and milk is given and an hour after, another skiagram is taken. If the bile passages and the gall-bladder are healthy,

a perfect picture of the gall-bladder is obtained: the last picture shows marked contraction of the gall-bladder caused by fat in the duodenum.

PHENIODOL has 51 of iodine in a tube of 4.5 gm. meal, or 3 g. suspension, for ready oral administration: said to cause minimal gastrointestinal or systemic disturbance and is believed to be safer.

The dye is also available in ampoules of 23 c.c. (1.75g.), 28 c.c. (3.5g) and 40 c.c. (5g.): about 3 to 4 g. may be given slowly intravenously. Films are taken 4, 8 and 24 hours after. The oral method is safer and fairly certain in effect and therefore intravenous route is seldom chosen.

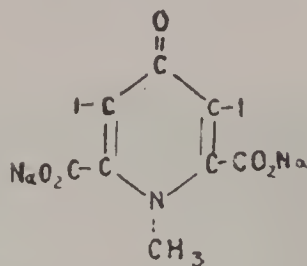
IODOXYLUM (*Iodoxyl*), $C_8H_3O_5NI_2Na_2$, Uropac

This, fairly well-known by the trade name, *Uroselectan B*, is the disodium salt of *N*-methyl-3:5-diiodo-4-pyridone-2:6 dicarboxylic acid, prepared by methylation of diiodochelidamic acid and subsequent conversion into disodium salt. It contains between 50.5 to 52.5% of iodine and 9.2 to 9.4% Na.

A white inodorous powder, soluble at 15.5° in 1.2 parts of water and 100 parts of alcohol (90%).

Dose, 150 to 225 grains or 10 to 15 grammes by intravenous injection.

Injectio Iodoxyli (*Inj Iodoxyl.*), See p. 44. Dose as of Iodoxyl. If the dose is not stated, 0.75 g. or 12 gr. per ml. is dispensed.



This is an organic iodine compound : given intravenously it is excreted into the kidneys without causing any local irritation and the kidneys become opaque to the X-rays. Skiagrams taken show the outline of the kidneys (*intravenous pyelography*). The special advantage is that the drug may be injected in a concentrated form. Fifteen grms. in 20 c.c. available in ampoules, slightly warmed to the body temperature is given slowly intravenously. Given in this form, the dye is better concentrated in the urine and a good shadow is obtained. The films are taken 12, 30 and 50 minutes after. The patient is prepared beforehand by adequately emptying the bowels, so as to lessen the gas collection.

This is quite safe unless there is gross disease of the liver or of the kidneys. This is suitable for children also.

This should be used cautiously in pulmonary tuberculosis, in persons with allergy or iodine idiosyncrasy.

Minor reactions as a feeling of thirst, generalised warmth and flushing of the face may occur.

INJECTIO DIODONI (*Inj. Diodon.*), Liquor Diodoni,
Perabrodil, Diodrast

Injection of Diodone is a solution of diethanolamine salt of 3:5-diiodo-4-pyridone-*N*-acetic acid in water for injection. Diodone is prepared by treating pyridine with thionyl chloride forming pyridyl-pyridinium chloride, hydrolysing to pyridone, iodinating and treating diiodopyridone with chloroacetic acid : 3:5-diiodo-4-pyridone *N*-acetic acid formed is made into diethanolamine salt.

It contains w/w 17.3 to 17.5% of iodine and between 34.7 to 35.5% of diethanolamine salt sterilised by filtration and distributed into ampoules or autoclaved : a clear and colourless fluid is obtained. Should be stocked away from light.

Dose by intravenous injection, 300 minims or 20 ml. for *adult*. 120 to 180 min. or 8 to 10 ml. for a *child* and 30 to 45 min. or 2 to 3 ml. for an infant.

Diodone B.D.H. in 35% solution and of Boots in 35, 50 and 70% solution are available in 3 and 20 c.c. ampoules.

Pharmacology [and Therapeutics]

Diodone in 35% solution slightly warmed, is very slowly injected intravenously in a dose according to age (*intravenous pyelography*).



Fig. 7.—The pelvis and the ureter of the kidney of both sides are visualised by pyelography with diodone

The adult dose is 20 ml. To small children the dye may be given intramuscularly or diluted with 4% normal saline, subcutaneously. The dye is excreted into the kidneys and makes the renal passages opaque to X-rays (**radiographic contrast agent**). Several Skiagrams are taken between 5 to 30 minutes after intravenous and 30 minutes to one hour after intramuscular injection. The dye may also be given by ureteral catheter (*retrograde pyelography*); 10 c.c. of a 20% solution is usually used. For visualising a fistula, a joint, uterus and the tubes, a smaller dose as 3 c.c. is introduced. A stronger solution (70%), *Uriodone forte*, is intended for arteriography and phlebography (visualising arteries especially cerebral arteries). Usual dose is 10 c.c. and 50 c.c. may visualise the chambers of the heart: for this a mixture of diethanolamine with diethylamine is preferred.

Although non-toxic and non-irritating, iodine sensitiveness should be tested by instilling a few drops into the eye. It is safer than iodoxyl. Intravenous administration of these iodine preparations are contraindicated in tuberculosis, hyperthyroidism and gross disorders of the liver and the kidneys.

ABRODIL or SKIODAN, 20 gram. in 50 c.c. of water (40%) used for pyelography.

VISKIOSOL SIX (diodone viscous solution) is used in hysterosalpingography.

OLEUM IODISATUM (*Ol. Iodisat.*). Iodised Oil, Lipiodol.

This is a compound of iodine dissolved in poppy seed oil prepared by treating poppyseed oil with hydriodic acid and put up in sterilised containers: has 39 to 41% of iodine. It is a colourless or light yellow, transparent, viscous oily liquid with a bland taste and alliaceous odour. It should be kept in a well-filled container protected from light.

This does not contain any free iodine and is bland and non-irritating. Being opaque to the X-rays, it is a **contrast**

medium for radiological examination of the bronchial tract: 20 to 30 c.c. of it are injected with a special curved needle into the trachea through the cricothyroid membrane or given orally through a cannula in the glottis: (the trachea being previously anæsthetised by an injection of $\frac{1}{2}$ c.c. of 5% cocaine solution). The oil enters into the different parts of the bronchi and bronchioles and their appearance is observed in the skiagram.

It has been introduced by cistern puncture into the thecal space and the spinal cord X-rayed (10% iodine solution is preferred). It has also been introduced into the uterus for X-raying the tubes. The oil remains at the site for 1 or 2 weeks, sometimes for a longer period.

NEO-HYDRIOL FLUID AND NEOHYDRIOL VISCOUS (M. & B.) in 2, 5, 10 and 15 c.c. ampoules and IODATOL (B.D.H.) in 5 and 20 c.c. ampoules may be used.

Symptoms of poisoning may appear in persons susceptible to iodine, especially if the oil is coughed out and swallowed. It should not be used on a case of pulmonary tuberculosis as systemic reaction may follow.

It is also sometimes prescribed for iodine action in 1 c.c. dose intramuscularly, increased to 10 c.c. in various arthritic, scrofulous, syphilitic and asthmatic conditions. Iodatol (10%) may be used.

Non-official Preparations

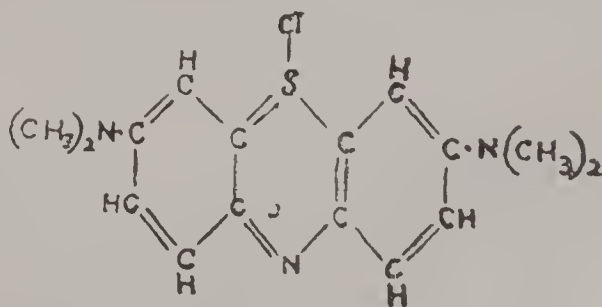
LIPIODINE (ethyl ester of diiodobrassicic acid) is also used for visualising the bronchial tree.

THOROTRAST.—This is a colloidal suspension of thorium dioxide and has recently been injected into the carotid and vertebral arteries. This causes opaque shadows of the blood vessels of the brain. By taking successive X-ray pictures, the rate of cerebral circulation, condition of the arteries and veins and deflection if any as happens by the presence of intracranial tumours are detected. It is also introduced directly into the ventricles and X-rayed.

METHYLTHIONÆ CHLORIDUM (*Methylthionin. Chlor.*)

Methylene Blue, $C_{16}H_{18}N_3ClS$

Methylene blue is tetra methylthionine chloride, prepared by the interaction of dimethyl-para-phenylenediamine with thiosulphuric acid, and oxidation of the product. A dark green crystalline powder with metallic lustre or dull dark green or brown inodorous powder: easily soluble in water and



alcohol (90%) and chloroform, making a dark blue solution.

Dose, 1 to 5 grains or 60 to 300 mg.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, Methylene blue is a weak **antiseptic** and is sometimes used for bladder irrigation in cystitis in 0·1 to 0·2% solution and as rectal wash in 1 in 1000 solution, less commonly for conjunctivitis and otitis media in 1 in 500 solution.

TAKEN INTERNALLY, it is excreted in the urine which is stained blue and exerts its **antiseptic** action on the urinary passages. [It is therefore sometimes prescribed in chronic gonorrhœa and tuberculosis of the urinary tract in 2 grs. doses either in pill or in capsule].

It is also used for testing the **kidney efficiency**. The rate of excretion is the test. 1 mil of 5% solution is injected into the lumbar muscles. If the kidneys are efficient, the urine should be pale green in $\frac{1}{2}$ hour. The colour deepens and continues to be blue for the 4 next hours. By cystoscopic examination, the efficiency of the two kidneys may be tested separately.

It is excreted with bile also and may have some antiseptic action on the **bile passages** but is seldom used for this purpose.

It is somewhat **analgesic** [and is sometimes prescribed for neuralgia, neuritis, migraine and rheumatic pain].

It is of some value in **cyanide poisoning**. A dose of 50 to 100 ml. of 1% solution is given intravenously. This converts ferrous iron of reduced hæmoglobin into ferric form and thus methæmoglobin is formed. This fixes the cyanide as stable nontoxic cyanmethæmoglobin. From this, cyanide is very slowly released and detoxicated by natural process. Nitrite thiosulphate treatment (p. 183) is more effective. Methylene blue is a useful **bacteriological stain** for microscopic examination.

INDICARMINUM (*Indicarmin.*), Indigo Carmine, $C_{16}H_8O_3N_2S_2Na_2$. Not official.—When 10 mils. of 1% solution containing 0·1 gramme of the dye is injected intramuscularly or 0·4% solution intravenously, it is quickly excreted in the urine. If the subject is now examined with the cystoscope, the dye appears in the bladder within 10 minutes in the former case and 5 minutes in the latter. The excretion is complete in 12 to 24 hours. [It is therefore used for testing the Kidney efficiency]. Delay in excretion indicates disease. The disadvantages are, (a) it is decomposed by purulent alkaline urine: (b) it is not capable of colorimetric estimation. It is now getting out of use.

PHENOL SULPHON-PHTHALEIN, *Phenol red*, Not official, in six mg. dose dissolved in 1 c.c. of water is also similarly given intramuscularly. Twenty minutes are allowed for the dye to reach the kidneys. The urine is collected 1 hr. 20 min. and 2 hrs. 20 min. after the injection and is treated with 25% caustic soda solution till made pink in colour. This is diluted with water to make 1 litre and the red colour matched with the standard solutions in the colorimeter. If the kidneys are efficient, in the first hour 45% and in the second 25% of the dye are excreted.

PART II

DRUGS USED MAINLY FOR SYSTEMIC ACTION

I. DRUGS HAVING GENERAL ACTION

AQUA DESTILLATA (*Aq. Dest.*), Distilled Water

Prepared by the distilling good, natural drinking water. It should be clear and transparent and have no smell and taste. It should not have more than the slightest trace of organic matter or ammonia and be free from metals, chlorides, sulphates and nitrates. If 100 mls be evaporated to dryness, the solid residue should not be more than 0.001 gram.

AQUA PRO INJECTIONE (*Aq. pro Inj.*) water for injection : Prepared by distilling potable water in a glass or a copper-free still : the first portion of the distillate is rejected and the remainder, collected in a sterile neutral glass container. This is closed by a non-absorbent cotton wool plug or by fusion of the glass and sterilised immediately by autoclaving. If closed with cotton wool, the water is used within a month and if sealed by fusion of glass, may be stored for a longer period.

If required for emergency, it is sterilised by boiling for thirty minutes and used within 24 hours.

Pharmacology [and Therapeutics]

Water, like air (oxygen) is essential for the existence of all living beings. A certain quantity of it is absolutely necessary for the normal upkeep of the body which diminishes or increases in the diseased state. It is used externally for bath and cleansing purposes and it is taken internally to make up for the daily loss of fluid by evaporation, urination, respiration, defæcation and other natural processes of elimination. A normal adult requires in cooler months about 2,000 c.c. of water per day. This he *obtains* (a) by drinking water, about 1300 c.c., (b) taken with food, about 1000 c.c. and (c) produces from metabolic products about 300 c.c. In warmer months, a much larger quantity is necessary. He *loses* (i) about 300 to 600 c.c. through the skin, (ii) 1200 to 1800 c.c. by the kidneys, (iii) 300 to 600 c.c. with the expired air and (iv) about 100 c.c. with the stool.

All living cells consist of colloids and different salts dissolved in water surrounded by a permeable membrane and outside the cells is the tissue plasma, also containing solutes and solvents in such a proportion that an osmotic balance is established. Most of the cells are permeable to water and to certain salts and the size and shape of the cells vary according to water contents. It is remarkable that although the fluid intake and excretion are constantly going on along with

variation in the colloids and saline constituents, this balance is never permanently disturbed including the percentage of the essential inorganic ions and this constitutes one of the principal vital phenomena of life. Absorption of nourishments, elimination of the excreta and cell reproduction require a free supply of water. A starving animal can live after losing all its glycogen and fat and half of its protein but a loss of 20% of water is rapidly fatal. (Rubner).

APPLIED EXTERNALLY, water slightly penetrates through the skin surface. So by prolonged immersion, the superficial epithelia are softened and swollen. Water enters more readily through the mucous membranes and so it act as irritant to the conjunctivæ and the nasal mucous membrane by causing a change of salt and fluid balance. Applied at a temperature below the blood-heat, as 75° to 80°F., water abstracts heat from the skin surface but reflexly increases the production of heat. Soon the loss exceeds the production and there is absolute fall in the temperature. After a stage of preliminary constriction, the cutaneous blood vessels dilate, the pulse and the respiration quicken causing a feeling of general well-being and exhilaration. Thus a bath has not only a general cleansing effect but it also acts as a stimulant to the entire system and thereby increasing the metabolic activity. Bathing is a daily practice of healthy people in India. Sudden sprinkling of cold water may act as restorative in syncope and stimulates the respiratory activities.

In a febrile condition, a **cold bath** or an **ice pack** is usually given for reducing the temperature and preventing hyperpyrexia. This has in addition a general sedative effect on the nervous system. If, however, the bath is continued too long, the skin becomes pale, the fingers shrivel up (goose-skin) and the heat loss may be excessive. In a febrile condition this may be followed by collapse. In others, superficial vasoconstriction causes visceral congestion which may aggravate an internal inflammation, if any, in the viscera.

A **tepid bath** at a temperature of about 100°F. is sometimes more pleasant but does not produce as much reflex effects. The cutaneous blood vessels dilate, often causing perspiration. The pulse and respiratory rates are increased. If the temperature is high, as in various febrile conditions, it is brought down, due to evaporation of water from the skin and also from prolonged radiation of heat from the dilated skin vessels which continues for sometime after the bath.

A **hot bath** at a temperature of about 103°F. dilates the cutaneous blood vessels even more, relieves vascular congestion and consequently pain and also muscular spasm; therefore it is helpful in infantile convulsion and in hepatic or renal colic. It induces perspiration and helps nitrogenous excretion when the kidneys are failing. The skin temperature may be slightly raised.

TAKEN INTERNALLY, water is the most harmless and **beneficial drink** for allaying thirst which is the expression of physiological demand for the replacement of the fluid lost through various excretory channels. It is the **best solvent** for many substances and therefore acts as a carrier of food to the tissues and also removes therefrom the waste-products of metabolism. These result in everchanging biochemical reactions which constitute the vital phenomena of life.

The ingested water passes through the stomach and is quickly absorbed mainly from the small intestine along with a large volume of fluid secreted by various digestive glands. The cæcum and the ascending colon absorb a certain amount and comparatively small amount only reaches lower colon and passes out with the faeces. Water increases the extracellular fluid volume and the blood volume. The blood consequently becomes hydræmic and colloids fail to retain so much fluid which is eliminated through the skin and the kidneys. This excretion is controlled by the pituitary and hypothalamus. The escape of the extra fluid from the blood is so quick in the healthy state that with normal food and drink, no obvious hydræmia results. This excess of fluid dilutes all toxins, extrinsic and intrinsic in circulation, causing their increased elimination also. A copious drink is a particularly useful **diuretic** when there is a tendency to formation of stones in the kidneys. The increased diuresis flushes the kidneys and minute particles of urates or oxalates, are less likely to be deposited as precipitate. A part of the fluid is excreted with the sweat causing **diaphoresis**. The muscles and the subcutaneous tissues also absorb a certain quantity of fluid which maintains their normal activity and these keep a **reserve** against sudden fluid loss. Increased water intake slightly increases the work of the kidneys and the heart. So oxygen consumption and elimination of nitrogen and sulphur appreciably go up.

A large tumblerful of water taken early in the morning, distends the small intestine, which starts peristalsis, hurries down its contents a little more rapidly into the colon and in certain cases **relaxes the bowels**. This is especially helpful when constipation is due to formation of hard scybalæ from too rapid absorption of fluid. But excessive drinking of water especially during meals is not beneficial, as the gastro-intestinal enzymes are much diluted, hampering the digestion.

If more water is absorbed than what is excreted, it accumulates in the body and eventually gives rise to toxic symptoms. Cells with an excess of fluid swell up: red blood corpuscles rupture and the tissue cells manifest pressure effects.

In a dog, an excess of water intake causes nausea, vomiting, headache, giddiness, hæmoglobinuria from breaking down of red blood corpuscles and lastly coma, convulsion and death.

In a human being also, this causes **nausea** and **vomiting** and **water** is sometimes used as a harmless emetic and the effects do not go any further. But other possibilities should be kept in mind when fixing up the quantity of an intravenous injection.

Distilled water is mostly used as solvent of various chemicals. *Water for injection* is the solvent of the different injections. It must also be "pyrogen free": the pyrogens are unidentified organic substances sometimes present in distilled water. If these are present in the injections, sharp febrile reaction may follow.

Double and triple distilled water in 5, 10 and 20 c.c. ampoules is available and often preferred for injection: these are often pyrogen free.

SODII CHLORIDUM (*Sod. Chlorid.*), Sodium chloride, NaCl

Colourless, transparent cubical crystals or white crystalline powder, soluble in 3 of water, prepared by purifying common salt. It contains not less than 99.5% of NaCl, dried at 130°.

Sodium chloride is an ingredient of *Inj. Sod. Cit. Anticoag.* and *Inj. Sod. Lact. Co.*

OFFICIAL PREPARATIONS.—(i) *Injectio Sodii Chloridi* (*Inj. Sod. Chlorid.*), Normal Saline Solution. See p. 47. The solution for injection is used within a month if the container is closed with cotton wool but if sealed by fusion, may be stored for a longer period. This is prepared with sterilised water. (iii) *Injectio Sodii Chloridi Compositus* (*Inj. Sod. Chlorid. Co.*), Ringer's solution. See p. 47.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

LIQUOR CHLORIDORUM TRIUM ISOTONICUS, Ringer's solution.—Sodium chloride 8.6 g., Potassium chloride 0.3 g., Calcium chloride 0.33 g. and distilled water recently boiled to 1000 ml. (*Nonsterile Isotonic Solution*).

A sterile solution is prepared by heating in an autoclave. A sterile solution for parenteral use is prepared with sterilised water for injection, placed in suitable containers and autoclaved.

Pharmacology [and Therapeutics]

This is the commonest and the most essential constituent of the extracellular body fluid, both sodium and chlorine ions being equally necessary: these are necessary for maintaining osmotic tension between the blood and the tissues.

In addition to oxygen, carbon, hydrogen and nitrogen which build up the organic portion of the body, 12 other elements are also essential for life. These are: calcium 1.5%, phosphorus 1%, potassium 0.35%, sulphur 0.25%, sodium 0.15%, chlorine 0.15%, magnesium 0.05%, iron 0.004% and manganese, iodine, fluorine and silicon (also probably copper) in minute traces. These are, however, distributed in a specialised way. Bones contain 99% of all Ca, and 75% P.: red blood cells 60% of Fe; thyroid, nearly all iodine; the tissue cells mostly K and the blood and tissue fluids Na and these maintain an isotonic balance. If these inorganic constituents are absent from the food which is the source of their supply, death follows quickly.

The normal life depends (a) on the *body fluid* maintaining the constant salt concentration with its similarly constant total volume also (b) on the *acid-base balance*. The body contains about 70 grammes of sodium, the large portion of which is in the blood and interstitial tissue fluid: 3 to 12 grammes of it are taken daily with food and a similar amount is excreted in the urine and sweats. The potassium content is about 150 grammes, all in the cells except 3 grammes in the body fluid. The minimum daily requirement is about 1 to 2 grammes of each, and a usual mixed diet contains 3 or 4 times of it. Vegetables contain more potassium than sodium and so the vegetarians require a larger quantity of common salt along with their normal diet.

The water and salt constant of the blood and of the tissue fluids is maintained by absorption, interchange and excretion of the excess mainly by the kidneys. The composition of the tissue-fluid (specially of the muscles and of the skin) can vary within a physiological limit, a certain mobile reserve of water and salts being retained there.

The water-constant is probably under the control of posterior pituitary and hypothalamus unit and sodium chloride, of suprarenal cortex.

Sodium exists mainly as chloride and potassium as phosphate. The subcutaneous tissues fix up a large amount of sodium chloride and is the chief chloride depot. The effects of a chloride poor diet are difficult to make out because such a diet is very unpalatable and not taken long enough. In an experimental condition, it is found that a certain proportion of the mobile reserve is lost and the salt excretion is rapidly reduced to salt intake. (Clark).

Neither the sodium nor the chlorine-ion has any definite specific action on any tissue and sodium chloride acts only by its physical property, namely, the **salt action**, maintaining an extracellular fluid and salt balance.

If given in an ISOTONIC (0.9%) SOLUTION, the sodium ion does not penetrate the cell-membrane but remains in the extracellular fluid. This dilutes the blood (hydræmia) and the extra fluid with salt is excreted by the kidneys causing diuresis. But the cells are unaffected. It has consequently no local action.

Sodium-ion by itself, would not support life. It is either insufficient or toxic to an isolated cell and minute quantities of calcium and potassium are necessary¹⁵⁹. To maintain the normal pH and prevent glucose from being washed out, a little of sodium bicarbonate and dextrose are also added.

(159) B

Ringer Locke Solution

Sod. Chlorid. 9

Pot. Chlorid. 0.42

Sod. Bicarb. 0.5

Calc. Chlorid. 0.24

Dextrosom 1

Aq. Pro. Inj. 1000

Given by the mouth, little absorption takes place from the stomach: it however improves the taste of various food-stuff and helps **secretion of gastric juice**. It passes down and is readily absorbed from the intestine. The fluid volume of blood and of interstitial tissue is increased causing dilution of blood colloid. If given per rectum in quantity not exceeding 4 to 8 fluid oz. at a time, it is often retained, absorbed and added to the blood volume which is of great value in many conditions of dehydration from loss of blood fluid: it re-establishes the normal circulation. If fluid loss has partly dehydrated the interstitial tissue also, such as of the muscles, the normal store is quickly restored. The extra fluid and salt if any, are eliminated to restore the normal blood volume. Ingestion of normal saline (0.5% solution is even better tolerated), therefore acts as a **diuretic**, to a less extent **diaphoretic**, and is remotely slightly **expectorant** also by liquefying the tenacious sputum.

This is specially suitable for **subcutaneous, intravenous or intraperitoneal injection**¹⁶⁰. Absorption from the serous cavities is more rapid than from the alimentary canal. Given intravenously, it causes much less rigor and reaction than that following injection of a hypertonic solution. [Sodium chloride solution isotonic or nearly so, is often combined with 5% dextrose or/and protein hydrolysate when fluid, saline electrolyte as well as nourishment are required as after profuse **hæmorrhage**, also loss of fluid and salt by **diarrhœa**, **vomiting** and profuse **perspiration**¹⁶¹. In severe hæmorrhage, Ringer's Solution is better as the normal salt constituents are more adequately restored. But as this dilutes the blood colloid and the fluid tends to escape, blood plasma is more preferred. In severe **toxæmia** as of an acute infective fever, the object is to dilute the toxin and favour its elimination through the kidneys and the skin by raising the capillary pressure. When **fluid intake** by the mouth is much **diminished** (as following a severe abdominal operation causing dehydration without much loss of salts), a solution containing 4.3% of dextrose and 0.18% of sodium chloride is preferred: 6 to 8 pints may be the total daily quantity. As long as the blood plasma has 540 to 620 mg.% of sodium chloride, it is not necessary to give any more sodium chloride and only 5% dextrose solution may do. If, to such a patient a large amount of saline solution is injected which cannot be excreted sufficiently rapidly, the tissue cells tend to get œdematous, especially in the bases of the lungs. But usually diuresis follows increasing the elimination

(160) R
Isotonic Saline Solution
 Sod. Chlorid. gr. 80
 (usually gr. 90)
 Pot. Chlorid. gr. 6
 Aq. pro Inj. pint one.

(161) R
 Sod. Chlorid. gr. 60
 Dextrosum gr. 137.5
 Aq. pro Inj. pint one.
 For subcutaneous or intravenous
 injection.

of water, urea, phosphates and other non-threshold substances also in addition to the extra sodium chloride].

HYPERTONIC SOLUTION.—*Applied locally*, it dissociates into two ions, sodium and chlorine, more readily than many salts : this along with its smaller molecular weight gives it great osmotic power. The salt being not penetrable, water is abstracted from the cells to make the fluid isotonic. If meat or fish is “**salted**” or placed in a concentrated salt solution, these become more or less dry and hard and so unsuitable for bacterial growth. [This is thus one of the harmless domestic methods of preserving food-stuff. For the same reason, for medico-legal purposes, post-mortem viscera are preserved in a saturated solution of common salt]. It may kill many bacteria and protozoa by abstracting fluid and is therefore an **indirect antiseptic**. A mineral spring bath in hypertonic salt solution or one prepared with 3 oz. of salt in a gallon of water (even sea-bath which is nearly isotonic), abstracts some fluid from the surface of the body. This, combined with the passage of a small quantity of salt into it, causes a mild irritation of the skin and is therefore **stimulating and refreshing**. Saline solution makes a good nasopharyngeal wash¹⁶². Applied to a wound surface it abstracts fluid from the surrounding tissue which lessens inflammation and helps to inhibit bacterial growth without damaging the tissues. But if very concentrated, it may cause **irritation and pain**. A concentrated salt solution is thus **hæmostatic** and **antiphlogistic** by its local astringent action on the tissues.

It is a direct chemical **antidote** to silver nitrate poisoning ; the precipitated silver chloride is bland and non-toxic.

Given Internally by the mouth in concentrated form, it acts as a local **astringent** on the mouth and the throat¹⁶³ by withdrawing fluid. The same action takes place on the stomach : the mucous membrane is shrivelled up and on account of some penetration of the salt, it causes **irritation and vomiting**. [Three to four teaspoonful of the salt in a pint of water is a harmless emetic in a non-corrosive chemical poisoning]. On the intestine also it exerts a certain amount of salt action and by collecting fluid, may act as a **purgative** ; but owing to its ready diffusibility in the intestine, this action is not as marked as that of a less diffusible salt. [If, however,

(162) R

Sod. Chlorid. 6

Pot. Chloras 1

Alum. 1

Acid Boric 1

Borax 6 (Martindale).

A tea-spoonful in half a tumbler of water for gargle.

(163) R

Borax gr. 3

Acid. Boric. gr. 1

Benzamin. Lact. gr. ½

Sod. Chlor. gr. 5

Sod. Benz. gr. ½

Menthol

Thymol. aa. gr. 1/100

Make Tablet : one in 2 fl. oz. of water for nasal douche.

2 to 3 pints of hypertonic salt solution be given per rectum, it relaxes the bowels more effectively. A similar enema is useful in expelling **thread worms** from the rectum].

Given Intravenously, the salt concentration of plasma is increased and it rapidly abstracts fluid from the tissue cells till the blood is made isotonic again. The blood colloids are diluted. The increased extracellular fluid and comparative dehydration of tissue cells are adjusted by eliminating the extra sodium chloride along with water keeping it in solution and the patient drinking more water. The effect is free **diuresis**, **sweating** and **thirst**.

In many cases of fluid loss especially from vomiting and diarrhoea, a certain amount of sodium chloride is also lost : this requires replacement of both salt and water and in these conditions, hypertonic saline may be indicated.

Hypertonic saline solution¹⁶⁴ was recommended by Rogers for the treatment of cholera and is very useful in the acute stage with much loss of fluid and lowered blood chloride. Increased osmotic tension of the blood causes quicker and freer exchange of fluid and salt, restoring the normal balance. Diarrhoea also tends to get less. [The quantity to be injected is determined by the specific gravity of blood, blood pressure and the clinical appearance of fluid loss : usually not more than 3 pints are necessary at a time].

If the solution is markedly hypertonic and the quantity is fairly large, death may follow from withdrawal of fluid from the central nervous system. But a small quantity as 50 to 75 c.c. of 15% solution when administered slowly intravenously, reduces the intracranial pressure and is useful in conditions with high blood pressure especially with cerebral symptoms (**encephalopathy**) or in cerebral tumour. The high tension of the blood and of cerebro-spinal fluid is lessened temporarily by causing a reverse osmotic tension.

In 1831, O'Shaughnessy introduced intravenous injection of physiological saline in cholera at Newcastle.

In a normal mixed diet about ten grms. of sodium chloride is taken daily and excreted by the kidneys and with sweat. The quantity is restricted only if its elimination is less than normal as in kidney diseases and in certain cases of high blood pressure. On the other hand, a prolonged want of it in diet tends to cause muscular weakness, anæmia and œdema.

(164) R

Hypertonic Saline Solution.

Sod. Chlorid. gr. 120

Calc. Chlorid. gr. 4

Pot. Chlorid. gr. 6

Aq. Steril. pint one.

(Sometimes Pot. Chlorid. is omitted).

For intravenous injection in cholera.

Acute sodium chloride depletion in the extra-cellular fluid causes (i) blood changes as rise in red blood cell count, hæmoglobin, red cell volume and plasma protein with lowered serum sodium: (ii) temporal regions, cheeks and eyes are sunken and (iii) anorexia, nausea and muscular cramps appear.

Recently a relationship between sodium metabolism and adrenal cortical insufficiency has been found. In adrenalectomised dogs and also in acute crisis of Addison's disease, blood sodium falls sharply. Such a crisis can be precipitated by withdrawing salt and mitigated by its administration. In cortical insufficiency, 2 to 10 gm. (usually 4 to 6 g). of sodium chloride are given daily by the mouth with benefit.

SUMMARY.—Sodium chloride is essential for extracellular osmosis influencing the movement of fluids and diffusion of salts. In diseases (a) with more fluid loss than salt, blood plasma or dextrose-saline and (b) with both fluid and salt loss, isotonic and occasionally hypertonic salt solutions (may be with dextrose also) are necessary. In cortical deficiency and in shock condition a plenty of sodium chloride is required.

II. ALKALIES

These are *hydrates* and *carbonates* of potassium, sodium and also of lithium. The active constituent of hydrates is OH. Carbonates and bicarbonates liberate CO_3 , are changed to HCO_3 and finally to OH and CO_2 : thus the final result is the same, only the change is slow. The chemical and pharmacological effects are also less violent with the carbonates and bicarbonates. In either case, *anion* and not *cation* is important.

POTASSIUM

1. POTASSII HYDROXIDUM (*Pot. Hydrox.*), Caustic Potash, KOH.

Prepared by the electrolysis of an aqueous solution of potassium chloride. White deliquescent stricks, freely soluble in water. Contains not less than 85% of total alkali as KOH and not more than 4% of K_2CO_3 .

Potassium hydroxide is an ingredient of *Liq. Cresol. Sap.*

LIQUOR POTASSII HYDROXIDI (*Liq. Pot. Hydrox.*), Caustic Potash solution. See p. 50.

INCOMPATIBLES.—Acids and acid salts, metallic salts, preparations of ammonia, alkaloids (which are precipitated) and especially the alkaloids of belladonna, hyoscyamus and stramonium (which are decomposed).

POTASSII CARBONAS (*Pot. Carb.*), Salt of Tartar, K_2CO_3 (Not official). White deliquescent powder, soluble 4 in 3 of water. Alkaline in reaction. Prepared by the interaction of potassium sulphate and calcium carbonate.

DOSE, 2 to 5 grains or 0.12 to 0.3 gramme.

2. POTASSII BICARBONAS (*Pot. Bicarb.*), Potassium Bicarbonate, *Yavakshara*, KHCO_3 .

White powder or crystals soluble at 15.5° in 4 of water. Saline taste and feebly alkaline; obtained by saturating strong aqueous solution of potassium carbonate with CO_2 .

DOSE, 15 to 30 grains or 1 to 2 grammes.

ACID NEUTRALISATION.—Potassium carbonate 60 grains neutralises 51 grains of citric and 54 grains of tartaric acids.

Potassium bicarbonate (60 grains) neutralises 42 grains of citric and 45 grains of tartaric acids.

3. POTASSII ACETAS (*Pot. Acet.*), $\text{CH}_3\text{CO}_2\text{K}$.

Obtained by the action of acetic acid on potassium carbonate. White deliquescent crystals or powders : soluble at 15.5° in 0.5 of water and in 2 of alcohol (90%). It must contain 99% of $\text{KC}_2\text{H}_3\text{O}_2$. Neutral in reaction.

DOSE, 15 to 30 grains or 1 to 2 grammes.

4. POTASSII CITRAS (*Pot. Cit.*), $\text{K}_3\text{C}_6\text{H}_5\text{O}_7\text{H}_2\text{O}$.

White, inodorous granular or crystalline powder with a saline taste obtained by neutralising solution of citric acid with pot. carb. Soluble in 1 of water.

DOSE, 15 to 30 grains or 1 to 2 grammes.

5. POTASSII CHLORIDUM (*Pot. Chlorid.*), Potassium Chloride, KCl .

Obtained from natural deposits or may be prepared by neutralising hydrochloric acid with potassium carbonate : contains not less than 99.5% of KCl , calculated with the substance dried at 130° .

Colourless, inodorous, cubical crystals or quadrangular prisms or crystalline powder with saline taste : soluble at 15.5° in 3 parts of water, insoluble in dehydrated alcohol.

DOSE, 15 to 30 grains or 1 to 2 grammes.

Potassium chloride is an ingredient of *Inj. Sod. Chlorid. Co.* and *Inj. Sod. Lact. Co.*

6. POTASSII NITRAS (*Pot. Nitras*), Potassium Nitrate, KNO_3 .

Obtained by interaction of sodium nitrate and potassium chloride : contains at least 99% of KNO_3 . A white crystalline powder or colourless crystals : inodorous with cool, saline taste : soluble at 15.5° in 4 of water.

DOSE, 5 to 15 grains or 0.3 to 1 gramme.

Pharmacology [and Therapeutics]

The positive-ion potassium exists in all cellular tissues of the animal body and is essential for the vital function. This ion is necessary for normal *cardiac action*, transmission of *nervous impulses* (both voluntary and autonomic) also for proper activities of the *skeletal muscles*. If kept on a diet deficient in potassium, death follows in about 22 days. Of the total of about 150 gm. of it in the human body, only 3 gm., (20 mg.%) are in the plasma and the rest in the intracellular fluid. As no other ion can take the place of potassium in the cells and cellular fluid has to be kept isotonic with extracellular fluid (potassium/sodium balance), the daily intake must fully compensate for the daily excretion. Potassium is obtained from vegetable and other foodstuffs taken every day.

It enters into the tissue cells very rapidly, including the red blood corpuscles and the extra amount passes out also as rapidly.

Therefore, in the usual doses taken by the *mouth* it does not produce any specific action of the potassium-ion and the only action shown is the salt action and special action, if any, of the negative-ion.

But potassium ion is highly toxic when present in the extracellular fluid even in concentration only one tenth of what is found in the cells. If given *intravenously* as potassium chloride, in a fairly big dose markedly raising the serum potassium level, it inhibits the activity of the heart, voluntary and plain muscles and also of the central nervous system. The *blood pressure* falls and the *heart* is somewhat slowed but



Fig. 8.—The heart is perfused with KCl (0.2%) solution



(Dixon)
Fig. 9.—The recovery of the heart after withdrawal of KCl

it dilates and quickens immediately after : with a bigger dose, the heart stops in diastole, the action being due to heart block and finally to ventricular fibrillation. The blood pressure rapidly falls mainly from direct action on the heart muscle : reflex vaso-dilatation from carotid sinus action has also some share. If injected into an artery to exclude the heart, blood pressure rapidly rises partly by peripheral vaso-constriction and partly by stimulation of the medulla and of the sympathetic ganglia. This “sympatho-adrenal phenomenon” is a complicated process.

The *voluntary muscles*, with a short period of increased activity becomes less responsive to stimulus. The automatic movements of the *plain muscles* become sluggish and these become contracted. The action is probably due to liberation of acetyl choline by stimulating the preganglionic fibres of the autonomic system. Potassium has some *anticurari* action also.

The activity of the *central nervous system* and also the reflexes are impaired and finally death follows from paralysis of the medulla. It is depressant to the peripheral nerves also, blocking nerve conduction. A concentration over 0.08% in the plasma is toxic which, however, is never obtained in therapeutic

oral administration. But caution is necessary in a case with marked renal insufficiency.

Given in a *smaller dose*, potassium salts have been found to increase the contraction of voluntary muscles acting directly on the muscles or through neuro-muscular apparatus. These are of value in certain familial periodic paralysis and in myasthenia gravis (Cushny).

In suprarenal gland deficiency, excretion of potassium is diminished. Adrenal cortex hormone is assigned to have important potassium metabolism regulating function. The symptoms of the disease may be attributable to potassium retention and its administration is restricted in such cases.

In paroxysmal tachycardia with extra-systole, a potassium salt is occasionally prescribed but is of doubtful value.

It will thus appear that potassium ion is *essential for the cell but toxic for the plasma*.

(1) **Alkalies** : HYDROXIDE (Caustic Potash), CARBONATE and BICARBONATE of Potassium.

All these act by liberating OH-ion. The carbonate and Bicarbonate dissociate in the body into CO_2 and KOH but as these do so only slowly, the Hydroxide, is a more powerful alkali than either of two :



The main actions of this group may be summed up as follows :

- (i) Dissolves proteins and makes them alkali-proteins,
- (ii) saponifies fats, (iii) abstracts water from tissues, if applied in a concentrated form. (iv) Neutralises acids and
- (v) exhibits salt action.

APPLIED EXTERNALLY, strong solution of the hydroxide is a powerful irritant and caustic, especially if applied in the form of a solid stick. This is due to its power of dissolving albumin and abstracting water from the tissues. As it forms soluble compounds with protein, no sufficient barrier is raised against its penetration and it often causes deep corrosion. [It is occasionally used for removing warts but not so suitable].

Carbonate is a less powerful alkali and bicarbonate is still less so.

These **saponify** oily secretions and potassium hydroxide is an emulsifying agent. These **dissolve the superficial horny layers** of the skin [and weaker solutions are used as **detergent** for cleaning purposes]. In a more dilute form, as $\frac{1}{2}\%$ of potassium hydroxide, **relieve irritation and itching** and probably act by neutralising or removing the irritant. [These are favourite applications for insect bites, caustic potash solution being usually chosen and in various skin affections as urticaria, a

carbonate or bicarbonate bath, usually 60 grains in one pint is given¹⁶⁵].

TAKEN INTERNALLY, the same local actions are produced on the mouth and the stomach and indirectly on the intestine.

On the mouth, these have an alkaline taste and a soapy feeling. The protective mucous coating and superficial epithelium being dissolved, these cause local irritation and the entire buccal cavity assumes raw red colour, more marked with a stronger solution (may cause even **corrosion**), than with a weaker one. [Bicarbonate 1 to 2% solutions are sometimes helpful as mouth wash, when there is acid corrosion of the teeth]. A still weaker solution is a reflex **sialogogue**.

On the Stomach, the same local action follows. A strong solution of hydroxide taken accidentally or for suicidal intention, causes corrosion: this may cause immediate death from perforation and shock or death follows some days after, from ulceration and cicatrization. Taken in a weak solution, these are **antacid**, acids in the stomach are neutralised and mucus is dissolved. From a carbonate or bicarbonate, CO_2 is liberated which slightly increases gastric motility and so acts as **carminative**. These are **mild local irritants** improving the blood supply and probably increases the **gastric secretions**. In practice, except bicarbonate, none of these are prescribed.

On the Intestine, there is no direct action. If hyperacidity is present, the alkalies tend to **hasten gastric emptying** by relaxing the pylorus.

On the other hand, if alkalies are taken too long without an interval and gastric juice continues to be of low acidity, sufficient pancreatic hormone is not produced lessening its secretions. In some cases **alkalosis** also follows.

Bicarbonate in moderately big dose is a **mild laxative** in some persons by the local salt action. These have no definite action on the biliary secretion.

ABSORPTION AND ELIMINATION.—Both hydrate and carbonate are absorbed into the blood mainly as sodium bicarbonate and although **available alkalies in the blood plasma increase**, its reaction as regards H-ion concentration does not alter.

The normal pH of blood is 7.2 to 7.4. The extreme range compatible with life lies between 7 (acidosis) and 7.8 (alkalosis).

Normally, the acids of metabolism (phosphoric, sulphuric and carbonic acids) and those of muscular exertion (lactic acid) are disposed of mainly in the urine and exhaled air, by protein and alkalies in the blood, mostly by sodium bicarbonate which is in larger quantity in the plasma.

(165) R

Pot. Carb.

Sod. Carb. each 3 oz.

Aq. Bull. gallons 20 (Middlesex).

For warm bath, in skin disease.

If, however, an excess of alkalies is taken, these combine with phosphoric acid to form the corresponding alkaline salt and during excretion, the urine has alkaline phosphate and bicarbonate and it becomes alkaline in reaction. So the blood, although has a larger quantity of available alkalies, by excretion, soon comes back to its normal condition.

Whenever any abnormal acid is produced and circulating in the blood such as β -oxybutyric acid and aceto-acetic acid (threatening acidosis), these alkalies are helpful in neutralising them thus sparing the blood alkalies¹⁶⁶.

URINARY SYSTEM.—Potassium bicarbonate taken orally increases the salt contents of blood which by abstracting fluid from the tissues, increases the volume of blood, dilates the arterioles causing **diaphoresis** and increase the glomerular pressure in the kidneys. More fluid along with this salt, therefore, collects in the renal tubules which although in excess, is not reabsorbed. An increased urinary secretion necessarily follows, which contains the ingested salt as well as other normal saline constituents of the urine. Being more diffusible than a sodium salt with a lower renal threshold, a potassium salt causes **better diuresis** than the corresponding sodium salt. But if on account of kidney disease, the excretion is delayed or if adrenal cortex deficiency is present, toxic effects of potassium-ion may follow. Potassium bicarbonate along with acetate and citrate is prescribed in gout and uric acid diathesis for causing diuresis which helps to flush out uric acid from the system¹⁶⁷. These are also useful in nephritis and acute gonorrhœa¹⁶⁸. The urinary solids are diluted and the irritation is soothed which gives relief]. Although the total nitrogen contents of the urine are unaltered, ammonia is diminished and urea is increased. The uric acid excretion is almost unchanged. Of the salts excreted, sodium salt generally predominates. But after a certain amount of it is lost, even with continued administration no further elimination takes place and the tissues are thus protected from the total loss of sodium which would be fatal: but at that stage, potassium excretion increases.

RESPIRATORY SYSTEM.—The alkalies after absorption, exhibit salt action on the bronchial glands, which makes the secre-

(166) R

Sod. Bicarb.

Pot. Bicarb. aa. gr. 240

Syr. Aurant. oz. 2

Aq. ad. pint one.

To drink freely.

For acidosis and also for acute toxæmia.

(167) R

Pot. Bicarb.

Pot. Acet. aa. gr. 20

Syr. Aurant. min. 60

Aq. ad. fl. oz. 1.

Every 4 hours.

For acute nephritis and gouty diathesis.

(168) R

Pot. Bicarb.

Pot. Acet. aa. gr. 20

Pot. Brom. gr. 10

Tinct. Hyoscy. min. 30

Syr. Aurant. min. 60

Aq. ad. fl. oz. 1

For acute gonorrhœa.

tion thinner, increased in quantity and easy of **expectoration**¹⁶⁹. [The bicarbonate is added to cough mixtures in bronchitis, especially if the secretion is tough and scanty].

SUMMARY.—Pot. hydrox. is a **caustic**, a **saponifying** agent and in weaker solution a **detergent**. Pot. bicarb. makes a soothing bath in skin affections : internally, it is an **antacid**, **diaphoretic**, **diuretic** and **expectorant** by local salt action.

VIENNA PASTE (Not official).—Caustic potash 5, slaked lime 6, made into paste with alcohol (90%). Used as a caustic.

(2) Neutral Salts : ACETATE, CITRATE and CHLORIDE OF POTASSIUM.

Being neutral, these have practically no local action either externally or internally and act mainly by salt action.

ACETATE AND CITRATE OF POTASSIUM

TAKEN INTERNALLY.—*In the stomach*, these are slightly decomposed by HCl and made into chloride. If taken in big doses, these may cause irritation and **vomiting** by salt action. *In the small intestine*, these are partly oxidised into carbonate and are absorbed as such. The systemic action is therefore much like that of a carbonate already described.



Thus, although their systemic action is from carbonates and bicarbonates, these do not interfere with the gastric acidity and this is an advantage. These are **diuretics** and **expectorants** and also to some extent **diaphoretics**, acting by their physical properties only (salt action) on the renal tubules, bronchial and skin glands. In these respects, these are a little more powerful than the corresponding sodium salts ; probably potassium ion has some specific irritant action (apart from salt action), at its points of exit. Being absorbed into the circulation as alkalies, these add to the **alkaline reserve** of the blood. The urine is made alkaline : to cause this, about 10 grams. of these daily may be necessary.

[These are frequently prescribed either alone or combined with carbonates and bicarbonates in nephritis (for diuresis), gout (for diuresis and elimination of the urates), catarrhal fevers (as diaphoretic)¹⁷⁰, in acidosis e.g., uræmia or diabetic coma (as pH balancer) and to render the urine alkaline in irritable condition of the urinary passages (as in acute gonorrhœa or B. coli bacilluria)].

Use of potassium salts in big doses for a long time as diuretic in Bright's disease is not without risk ; retention may

(169) R
Pot. Bicarb. gr. 20
Pot. Cit. gr. 15
Sp. Ammon. Aromat. min. 20
Syr. Tolu. min. 60
Aq. Camph. ad. fl. oz.
For acute bronchitis.

(170) R
Pot. Acet.
Pot. Cit. aa. gr. 15
Pot. Bicarb. gr. 20
Sp. Chlorof. min. 20
Aq. Camph. ad. fl. oz. 1
A diaphoretic and diuretic.

take place causing specific action of potassium-ion in increasing cardiac failure. Further, Potassium salts are not to be used in suprarenal cortical deficiency.

The citrate is not as readily absorbed as the acetate and therefore, if given in big doses, may act as a mild **purgative** by salt action on the bowels.

Over 95% of the acetate and citrate is oxidised and only 2 to 3% is absorbed as such and excreted in the urine unchanged. The citrate forms a compound in the blood, calcium citrate, which does not ionise. It therefore fixes up a part of blood-calcium which, if large enough, **retards the coagulation** of blood.

SUMMARY.—Pot. acet. and Pot. cit. are systemic **alkalisers** and often used as **diaphoretic, diuretic and expectorant** acting by salt action.

POTASSIUM CHLORIDE

Potassium chloride is recently be used for the specific action of potassium ion. This ion has been found to stimulate the formation of or enhance the **action of acetylcholine**. In certain types of familial paralysis, during the attack, serum potassium level falls, may be below 12 mg%. To them pot. chloride in doses of 5 to 10 grm. daily usually gives a clinical cure. Similar benefit follows in myasthenia gravis.

In **Meniere's disease**, daily doses 2 to 5 grm. or more causes improvement. The mode of action is uncertain, may be by causing a difference of electrolytic composition of the plasma.

In **allergy**, potassium chloride 4 to 6 grm. daily with low sodium intake is useful especially in urticaria : it is sometimes prescribed in migraine also.

MIGAPON tablets, *Not official*, each containing pot. chlorid. 2.15 gr. and calc. lact. 2.85 gr. (approximately the same ratio as in the tissue), 4 to 6 well diluted in water, taken before the attack is helpful in migraine (normal blood volume is restored with vascular relaxation).

In **nephritic œdema**, potassium chloride is a substitute for sodium chloride being more readily excreted.

NEO-SELAROM (Bayer product) contains pot. and ammon. chlor., pot. and calc. format. and mag. cit. and has an agreeable salty flavour : is used as sodium chloride substitute.

Potassium chloride is a constituent of the compound injections of sodium chloride and sodium lactate.

POTASSIUM NITRATE.—This is a *diuretic* and *diaphoretic*, acting mainly by local salt-action. But given in bigger doses, and in concentrated form, it is *irritant* to the gastrointestinal tract and to the kidneys. This is now seldom prescribed.

The fumes of burnt potassium nitrate often combined with stramonium leaves, are useful in relieving the paroxysms of bronchial asthma. The nitrate is made into nitrite which acts as a *broncho-dilator*.

Pot. acet., pot. nit. and formalin in suitable proportion (*Kaiserling's solution*) is used for hardening and preserving pathological specimens.

SODIUM, (Na)

1. SODII HYDROXIDUM (*Sod. Hydrox.*), Caustic soda, NaOH .

This is obtained by the electrolysis of watery solution of sodium chloride. It must contain not less than 95% of NaOH .

Very deliquescent, hard sticks or masses: rapidly absorb CO_2 and soluble in 1 part of water.

This is an ingredient of *Mist. Mag. Hydrox.*

2. SODII CARBONAS (*Sod. Carb.*), Washing soda, $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$.

It is prepared by the action of heat on sodium bicarbonate and subsequent crystallisation from water. It contains between 99 to 105% of $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$. Transparent, colourless, efflorescent, rhombic crystals, inodorous with strongly alkaline taste. Soluble in 2 parts of water, insoluble in alcohol 90%.

Sodium Carbonate is used in the preparation of *Ferr. Carb. Sacch.* and *Liq. Sod. Chlorinat. Chir.*

3. SODII CARBONAS EXSICCATUS (*Sod. Carb. Exsic.*), Na_2CO_3 .

Prepared from sodium carbonate by driving away the water of crystallisation by means of heat. A white powder with strongly alkaline taste and readily soluble in water.

This is an ingredient of *Pil. Ferr. Carb.*

4. SODII BICARBONAS (*Sod. Bicarb.*), Sodium bicarbonate, NaHCO_3 .

Prepared by the interaction of sodium chloride and ammonium bicarbonate, containing between 99 to 101% of NaHCO_3 . Occurs in small white crystals or powders, inodorous, alkaline and salty to taste and soluble in 11 of water and insoluble in alcohol 90%.

Dose, 15 to 60 grains or 1 to 4 grammes.

INCOMPATIBLES.—Acids, acid salts (liberate carbon dioxide) and alkaloids (these are precipitated).

Sodium carbonate (60 grains) neutralises citric acid 29½ grains and tartaric acid 31½ grains.

Sodium carbonate 60 grains neutralises citric acid 50 grains and tartaric acid 53½ grains.

(i) *Injectio Sodii Bicarbonatis* (*Inj. Sod. Bicarb.*) See p. 47.

(ii) *Tabellæ Sodii Bicarbonatis Compositæ* (*Tab. Sod. Bicarb. Co.*), Soda Mint Tablets. See p. 58.

5. SODII CITRAS (*Sod. Cit.*), Sodium citrate, $\text{C}_6\text{H}_5\text{O}_7\text{Na}_3 \cdot 2\text{H}_2\text{O}$.

This is obtained by the interaction of citric acid and sodium carbonate. It contains 99% of $\text{C}_6\text{H}_5\text{O}_7\text{Na}_3 \cdot 2\text{H}_2\text{O}$.

White, inodorous, granular crystals or crystalline powder with salty taste: slightly deliquescent in moist and efflorescent in warm dry air: soluble in less than 2 parts of water.

Dose, 15 to 60 grains or 1 to 4 grammes.

OFFICIAL PREPARATIONS.—(i) *Injectio Sodii Citratis Anticoagulans* (*Inj. Sod. Cit. Anticoag.*). See p. 47. If kept in a container with cotton wool

plug, this is used in a month : if sealed by fusion of glass, may be kept for a longer period. (ii) **Injectio Sodii Citratis cum Dextroso** (*Inj. Sod. Cit. c. Dextros.*). See p. 47. If kept separate as 30 g. of sodium citrate dissolved in 900 ml. of water for injection, during use, to 5 of citrate solution 1 of dextrose solution is added. (iii) **Tabellæ Sodii Citratis** See p. 53.

DOSE, as of Sodium Citrate.

6. **INJECTIO SODII LACTATIS COMPOSITUS** (*Inj. Sod. Lact. Co.*) Hartmann's or Ringer-Lactate solution. (See p. 47).

SODII LACTAS (*Sod. Lact.*), Sodium lactate, $\text{CH}_3\text{CHOHCOONa}$, Not official.—This prepared by adding sodium hydroxide or carbonate to a hot solution of lactic acid and subsequent concentration containing 68 to 72% $\text{C}_3\text{H}_5\text{O}_3\text{Na}$.

A clear colourless or pale yellow viscous liquid with slight odour and saline taste. This was used in $\frac{1}{2}$ molar solution for *acidosis*.

Pharmacology [and Therapeutics]

Sodium ion activates the suprarenal cortex and probably potassium ion, the medulla. So in conditions treated with suprarenal medullary extract (adrenaline chloride) like asthma, urticaria and œdema, low Na-intake in the diet has been advised (as flour, cream, sugar, potato, squash and many green vegetables and milk) and potassium chloride is given orally. In conditions of Cortical deficiency, on the other hand, potassium is restricted and sodium salts are freely given.

Sodium-ion is bland and has no specific action on any tissue. The alkaline salts of sodium, as sodium hydrate, carbonate and bicarbonate have the same action as the corresponding potassium salts except that the sodium-ion is more slowly absorbed and excreted and it does not penetrate into the tissue cells (See p. 240). Of the sodium salts, the bicarbonate, is more popular than the corresponding potassium salt.

APPLIED EXTERNALLY, sodium carbonate in 0.5% solution is frequently used as a bath in various skin diseases to **relieve itching** and for general **cleansing** effect. The bicarbonate is largely used with various antiseptics to irrigate many mucous surfaces, especially that of the nose (p. 80 and 243).

TAKEN INTERNALLY, sodium bicarbonate **neutralises acids** in the stomach in various conditions of hyperacidity, heart-burn and acid pain. The relief is very prompt but as its effects are short-staying, it is profitably combined with insoluble carbonates of calcium and magnesium which are more slowly neutralised.¹⁷¹ This interaction of the acid with alkalies, especially with sodium bicarbonate is often followed by further secretion of acid and evolution of CO_2 and the ultimate effect has not been found favourable.

Further, a prolonged administration of these, as is necessary in gastric ulcer, causes **alkalosis**. Consequently magnesium

(171) B

(a) Sod. Bicarb.

Mag. Oxid. Pond. aa. gr. 10. Pulv.

(b) Sod. Bicarb. gr. 30

Creta gr. 10. Pulv. Original Sippy formula.

One every half hour between feeds. This however is now seldom used.

oxide and trisilicate and aluminium hydrate (acid-adsorbants) are more frequently used than direct alkalis. See p. 213.

ACIDOSIS, ALKALOSIS.—On account of certain substances present in the blood, especially bicarbonates and plasma protein and hæmoglobin called *buffers* which can take up or part with a large quantity of acids without causing any marked change, the pH of blood is kept constant. An alkali in excess is thrown out by the kidneys in combination with phosphoric acid. Further, blood urea and aminoacids by being or not being changed into ammonia also help this mechanism. If for any reason the compensation fails in either way, the blood becomes either hyperalkaline (alkalosis), neutral or acid (acidosis) and death follows.

Sodium bicarbonate is prescribed in acid dyspepsia with poor appetite and considerable secretion of mucus. It promptly **dissolves the mucus** and favours the secretion of normal gastric juice and acts as a **carminative**¹⁷² also.

Sodium bicarbonate, 5% solution in normal saline, is frequently given by the mouth as well as intravenously, for **acidosis**,¹⁷³ in diabetic coma, cholera and in threatened uræmia. For intravenous injection, it should preferably be sterilised by autoclaving in the form of dry powder and dissolved in water for injection than boiling it in watery solution: boiling makes some sodium carbonate which is toxic intravenously.

COMPOUND SODIUM LACTATE SOLUTION is also administered intravenously for acidosis to rapidly overcome alkali deficiency. It is better than sodium bicarbonate solution, more readily sterilised and will not cause tissue necrosis if escapes into the subcutaneous tissue. Further slow conversion of sodium lactate into bicarbonate obviates the danger of alkalosis.

SUMMARY.—*Externally* sod. carb. is used in baths and bicarb. as wash for mucous surfaces. *Internally*, bicarbonate is antacid and carminative and systemic alkaliser (for this sodium lactate compound is preferred).

SODIUM CITRATE

Sodium Citrate has the same action as Potassium Citrate but is a little less diffusible. It is a **diuretic**¹⁷⁴⁻¹⁷⁵, **mild diaphoretic**¹⁷⁶ and **expectorant** due to its salt action after absorption but is less frequently used than potassium citrate.

(172) R

Sod. Bicarb. gr. 15

Tinct. Nuc. Vom. min. 10

Tinct. Cardam. Co. min. 20

Inf. Calumb. ad. fl. oz. 1

Mix. One hour before food, for acid dyspepsia.

(173) R

Sod. Chlorid. gr. 90

Sod. Bicarb. gr. 160

Aq. Steril. pint. one.

For intravenous injection.

Rogers' alkaline saline (for cholera).

(174) R

Sod. Cit.

Pot. Cit. aa. gr. 20

Sp. Æther. Nitros. min. 20

Syr. Aurant. min. 60

Aq. Chlorof. ad. fl. oz. 1

A diaphoretic and diuretic.

(175) R

Sod. Cit.

Pot. Cit.

Sod. Bicarb. aa. gr. 10-60

Syr. Aurant. min. 60

Aq. Chlorof. ad. fl. oz. 1

For acute nephritis.

In big doses, it is a mild **aperient** from its salt action on the intestine.

The citrate-ion combines with calcium and **retards the coagulation** of blood : 0·5% of sodium citrate in blood is sufficient to prevent clotting. [Therefore 32 c.c. of 3·3% solution (which is isotonic), are added to every 100 c.c. of blood during transfusion to prevent clotting. (This contains roughly 0·9% of sodium citrate which is quite safe). This if stored at 4°C. (blood bank), keeps well for about three weeks. (Clark).

The quantity of sodium citrate used may vary but it should be at least 0·3 grm. or 8 c.c. of 4% solution per 100 c.c. of blood.

SODIUM ACID CITRATE (Not official), 1·7 to 2% with 2·5% dextrose, autoclaved, is a more suitable anticoagulant.

The syringes and other apparatus are washed out with 3·8% solution before the collection of blood.

Sodium citrate is sometimes added to boiled milk, (1 to 2 grains per ounce) ; a part of calcium is inactivated and the milk does not form a dense coagulum in the stomach. [Such milk is helpful in gastro-duodenal ulcer and also for infants suffering from indigestion].

A 5 to 30% sol. intravenously or 30% sol. 15 c.c. intramuscularly tends to increase coagulation of blood : now seldom used therapeutically.

SODIUM ACETATE (Not official), has the same action as pot. acet. and prescribed in 15 to 30 gr. doses.

OTHER ALKALIES

Calcium hydrate, Calcium carbonate, Ammonia, Ammonium carbonate and bicarbonate are also alkaline in reaction and act as alkalies at the site of application. But as these on account of their *cation* have important local and systemic actions also, these have been described in another place.

Non-official Preparations

LITHIUM SALTS.—The Citrate (Dose, 5 to 10 grain) and Carbonate (Dose, 2 to 5 grains) of Lithium act like similar salts of Potassium, and in the same way add to the alkaline reserve of the blood and are also slightly depressant to the muscles. These are rapidly absorbed from the stomach and excreted, to some extent through the salivary glands, stomach and intestines but mostly through the kidneys causing diuresis. The last although rather slow is not associated with any irritation. The urine is made alkaline¹⁷⁷.

But these to some extent irritate the stomach and the intestine, and if the dose is fairly big, there may be marked gastro-enteritis, causing nausea, vomiting and diarrhoea.

(176) R

Sod. Cit.

Pot. Cit. aa. gr. 20

Tinct. Ipecac. min. 10

Tinct. Scill. min. 5

Syr. Tolu. min. 60

Aq. Camph. ad. fl. oz. 1

Diaphoretic and expectorant

(177) R

Lith. Cit. gr. 10

Pot. Cit. gr. 20

Liq. Ammon. Cit. Dil. min. 60

Tinct. Aurant. min. 20

Inf. Scopar. ad. fl. oz. 1

A diuretic for gouty diathesis.

Lithium salts were formerly very much given for *Uric Acid Diathesis* as solvent for sodium biurate in gouty joints, with the hope that Lithium biurate would be formed which being freely soluble, would be excreted by the kidneys. But a concentration of these in the blood that could be of any use as a solvent, is unattainable owing to toxic effects and hence are hardly much used.

THIALION.—Contains sulphates, citrates and chlorides of sodium and potassium and lithium citrate. A laxative lithia compound.

DOSE, 1 tea-spoonful every morning in 4 oz. of water.

WEST SAL, lithium chloride, is sometimes used as salt substitute in food but if used for a long time, may cause toxic symptoms.

III. ACIDS

1. ACIDUM HYDROCHLORICUM (*Acid. Hydrochlor.*), HCl. Hydrochloric acid, Muriatic acid.

Sodium chloride is acted on by sulphuric acid: the gas so formed (hydrogen chloride) is dissolved in water; a strongly acid, colourless, fuming liquid is formed: contains 35 to 38% w/w of HCl.

INCOMPATIBLES.—All alkalies and alkali salts, lead and silver salts.

Acidum Hydrochloricum Dilutum (*Acid. Hydrochlor. Dil.*), See p. 36.

DOSE, 5 to 60 minims or 0.3 to 4 mls.

2. ACIDUM NITRICUM (*Acid. Nit.*), Nitric Acid. HNO_3 .

Prepared by the action of sodium nitrate and sulphuric acid or by synthesis, the fumes being distilled over. It is a colourless or yellowish fuming liquid with corrosive fumes. It contains 70% w/w of HNO_3 .

INCOMPATIBLES.—All alkalies and alkali salts, oxides, iron sulphate, lead acetate and alcohols.

Nitric acid is used in the preparation of *Ung. Hydrarg. Nit. Dil.* and *Ung. Hydrarg. Nit. Fort.*

3. ACIDUM PHOSPHORICUM (*Acid. Phosph.*), H_3PO_4 .

A colourless, inodorous syrupy liquid, prepared by the oxidation of phosphorus in contact with water. It contains 89% of H_3PO_4 .

INCOMPATIBLES.—All alkalies, sodium carbonate, calcium salts.

Acidum Phosphoricum Dilutum (*Acid. Phosph. Dil.*), See p. 36.

DOSE, 5 to 60 minims or 0.3 to 4 ml.

4. ACIDUM HYPOPHOSPHOROSUM DILUTUS (*Acid. Hypophosph. Dil.*), Dilute Hypophosphorous Acid, H_3PO_2 .

Prepared by the interaction of barium hypophosphite and dilute sulphuric acid. A clear, colourless inodorous acid liquid containing 10% w/w of H_3PO_2 . Miscible with water and alcohol (90%).

DOSE, 5 to 15 minims or 0.3 to 1 ml.

5. ACIDUM ACETICUM (*Acid. Acet.*), Acetic acid.

Prepared by destructive distillation of wood and also by dilution of glacial acetic acid: contains about 33% w/w of hydrogen acetate, $\text{HC}_2\text{H}_3\text{O}_2$. A clear, colourless liquid with pungent smell and sharply acid taste.

OFFICIAL PREPARATIONS.—(i) **Acidum Aceticum Dilutum** (*Acid. Acet. Dil.*), See p. 36. (ii) **Oxymel**, See p. 51. **DOSE,** 30 to 120 minims or 2 to 8 ml.

6. ACIDUM ACETICUM GLACIALE (*Acid. Acet. Glac.*), Glacial Acetic Acid, $\text{CH}_3\text{CO}_2\text{OH}$.

Prepared either by the action of sulphuric acid on an acetate or synthetically: a clear colourless fluid with a pungent smell. It contains

not less than 99% of $\text{HC}_2\text{H}_3\text{O}_2$. Miscible in water and in most fixed and vegetable oils.

It is used in the preparation of *Liq. Ammon. Acet. Fort.* and *Dil.*

7. **ACIDUM TRICHLORACETICUM** (*Acid. Trichlor. Acet.*), $\text{CCl}_3\text{CO}_2\text{H}$.

Prepared by the oxidation of chloral with nitric acid, containing not less than 98% of $\text{C}_2\text{HO}_2\text{Cl}_3$: colourless very deliquescent crystals or crystalline mass with a characteristic pungent smell. Freely soluble in water, alcohol (90%) and in solvent ether.

8. **ACIDUM CITRICUM** (*Acid. Cit.*), Citric acid, $\text{H}_3\text{C}_6\text{H}_5\text{O}_7\text{H}_2\text{O}$.

Obtained from the juice of various species of Citrus or from glucose. It must contain not less than 99.5% and not more than 101% of hydrogen citrate. Colourless, odourless crystals or white powder with strongly acid taste, very soluble in water.

Dose, 5 to 30 grains or 0.3 to 2 grammes.

Citric acid is used in the preparation of *Syr. Limon.*

INCOMPATIBLES.—Alkaline carbonates, acetates and pot. tartrates.

10. **ACIDUM LACTICUM** (*Acid. Lact.*), Lactic acid, $\text{C}_3\text{H}_6\text{O}_3$.

A colourless or slightly yellow, hygroscopic syrupy liquid obtained by fermentation of lactose and is freely miscible with water, alcohol and solvent ether. Contains Lactic acid and lactide to 87.5% w/w of $\text{C}_3\text{H}_6\text{O}_3$.

Lactic Acid is used in the preparation of *Inj. Sod. Lact. Co.*

11. **ACIDUM TARTARICUM** (*Acid. Tart.*), Tartaric acid, $\text{H}_2\text{C}_4\text{H}_4\text{O}_6$.

It is obtained from potassium acid tartrate. It should contain not less than 99.5% of hydrogen tartrate dried at 100°. Colourless crystals or white powder with no smell but a strongly acid taste. Soluble in less than one of water, 2.5 of alcohol 90% and slightly soluble in ether.

Dose, 5 to 30 grains or 0.3 to 2 grammes.

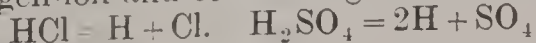
Tartaric Acid is used in the preparation of *Pulv. Efferv. Co.* and *Inj. Adrenal.*

INCOMPATIBLES.—All alkalies, salts of potassium, calcium, lead, mercury and vegetable astringents.

NEUTRALISATION.—Tartaric Acid 10 parts requires ammon. bicarb. 11, mag. carb. 6.5, pot. bicarb. 13.25 and sod. bicarb. 11.25 parts to neutralise.

Pharmacology [and Therapeutics]

In watery solution all these acids are dissociated into a positive hydrogen-ion and certain negative ion as



The characteristic acid properties are really due to dissociability of the hydrogen-ion. Strong mineral acids as the sulphuric, nitric, hydrochloric and phosphoric acids are powerful owing to their easily dissociable hydrogen-ion.

Among the organic acids, acetic, trichloroacetic and lactic acids are strong. Citric and tartaric acids are feeble, citric being the feeblest.

There are other acids again. An acid like hydrobromic or hypophosphorous acid is used partly for its acid ion and partly for the base. But an acid like hydrocyanic or salicylic acid does not show as much acid action as that of the powerful base. These two will be taken up in another place.

GENERAL ACTIONS OF ACIDS

The pharmacological action of acids may be divided into two groups, **local**, directly on the spot these come in contact with and **systemic**, on the alkaline reserve of the blood.

LOCAL ACTION.—All living tissues except some vegetable organisms are faintly alkaline in reaction and any marked alteration of their hydrogen-ion concentration causes death. Thus all acids, if strong enough to do this are protoplasmic poisons and **antiseptic**, so much so that most of them, especially the mineral acids, inhibit bacterial growth in even 0.2 to 0.5% dilution.

Concentrated acids **neutralise** all **alkalies**, have a great **affinity for water** and **precipitate protein** especially globulins. These are thus powerful **caustics**. So while the alkalies make a surface swollen and smooth to touch, acids make it white, dry and rough : finally, the place becomes brown or black, according to the severity of the caustic action.

If the acid is milder in action, owing either to dilution or its weaker properties, the effects are mitigated. Thus, instead of being caustic, it is an **irritant** and causes **local vasodilatation**. If applied on the skin, it acts as a **rubefacient** and if kept longer, it is a **vesicant**.

A dilute solution of an acid is a feeble irritant [and may be used as a **counter-irritant** being applied on the skin over chronically inflamed viscera]. By coagulating protein and by its local **astringent** effects on the blood vessels, it acts as a **hæmostatic**. [Dilute sulphuric acid is sometimes used to control capillary oozing as from a leech bite]. In more dilute solution, these are used to check local sweating (**anhidrotic**).

In the same way, a bath in weak acids as in vinegar, is a **refrigerant** and sometimes helpful in fever.

NITRIC ACID concentrated, applied on the skin, oxidises and coagulates protein forming nitroproteins : these stain the skin yellow. The coagulated protein not being readily soluble, forms a barrier to much deeper penetration of the acid. It is therefore more suitable for therapeutic use as a **caustic**.

[Infective sores as condylomata, phagedænic ulcers or cancrum oris are lightly touched with fuming nitric acid followed by 95% alcohol : so also the wound caused by the bite of a rabid animal : the rabies virus is often thereby destroyed. Warts are also sometimes cauterised with it but salicylic acid paste is more popular].

HYDROCHLORIC ACID concentrated liberates irritating fumes which if much, may cause rapid death from asphyxia or may lead to spasm of the glottis or œdema of the larynx. It is less corrosive than the previous two. **PHOSPHORIC ACID** is the feeblest mineral acid. These are not used externally for any therapeutic purpose.

The Organic Acids which are not as readily dissociated, have less powerful action on the intact skin and even on the mucous membranes and are therefore more suitable for milder caustic action.

ACETIC ACID is sometimes used as a caustic but more frequently as a *rubefacient* in liniments. It is sometimes applied on a ringworm patch, but painful. Vinegar may be an antidote for alkali poisoning. Dilute acid used as oxymel is a cough linctus.

LACTIC ACID in 50% solution is sometimes applied on the larynx, throat and tongue in malignant ulcers. In weaker as 10% solution, it is *astringent*,¹⁷⁸⁻¹⁷⁹ and in 2 to 3% solution is used as a vaginal douche ; in 2% jelly, as a *contraceptive*.

TRICHLORACETIC ACID is sometimes used as a *caustic* [for foul sores], as *counter-irritant* [being applied in 20% solution on leprotic patches] and in weaker solution (1 to 2%) as *astringent* wash for stomatitis or for gonorrhœa.

TAKEN INTERNALLY, the local action of the acid on the mucous membranes is much greater than that on the skin. If the acid is fairly strong, in addition to mouth, throat, œsophagus and stomach are much corroded. Death may follow rapidly from perforation of the stomach and intestine and from shock or be deferred till the remote effects appear. The ulcerated area heals and is converted into a scar permanently impairing gastric secretion or causing pyloric stenosis.

Mouth.—Dilute acids have a peculiar agreeable taste which increases the **salivary secretion** and reflexly, the gastric secretion [Organic acids form important constituents of pickles. For anorexia, these are largely used as appetiser. Citric acid in the form of lemonade and fresh lime-juice is frequently made into cooling drinks. Lactic acid 60 min. in one pint of milk (sour milk) is sometimes prescribed for diarrhœa and colitis].

Stomach.—In addition to favouring **reflex gastric secretion**, the dilute acid, especially the hydrochloric is frequently used for hypo-acidity of the stomach. But normal gastric

(178) B

Acid. Lact. min. 30

Aq. Dest. ad. fl. oz. 1

For throat paint in follicular tonsillitis.

(179) B

Acid. Lact. fl. oz. $\frac{1}{2}$

Formalin min. 30

Phenol gr. 44

Glycer. ad. fl. oz. 8

For cauterizing the nose and the throat cavity.

secretions are reduced by its astringent action if in concentration above 0.2%. It is a gastric **antiseptic** also.

[It is useful in hypo-acidity of tuberculosis, sprue and in convalescence from prolonged acute febrile conditions like typhoid fever¹⁸⁰⁻¹⁸¹. It is also prescribed in achylia gastrica and in pernicious anæmia : as a large quantity of acid is required, 120 min. of dilute hydrochloric acid in 4 oz. of water is slowly sipped for two hours after a meal.

In cases of "acidity," from acids of gastric fermentation, administration of dilute HCl immediately after food is beneficial, checking putrefaction by acting as an antiseptic].

Betaine Hydrochloride (Trimethylglycine hydrochloride), Not official, readily liberates hydrochloric acid and is convenient to take dissolved in water in 3 to 8 gr. doses.

Other portions of the Alimentary Canal.—The acid chyme, as it reaches the duodenum, acts as hormone to the liver and the pancreas, favouring the **secretion of bile and pancreatic enzymes**.

Thus in a suitable case, an all round beneficial effect on the entire digestive tract is produced.

A dilute acid is of some value in diarrhœa¹⁸² for its slight astringent action on the intestine and dilute sulphuric acid is occasionally prescribed].

Lactic Acid Milk is prepared by adding 45 to 60 minims of lactic acid to a pint of milk which should be stirred vigorously to prevent formation of big clots : a fine flocculent curd is formed which can pass through the rubber teat of the bottle and is an easily digestible infant food.

Citric and tartaric acids are sparingly absorbed and act as mild **aparients** by local salt action. These are often used as effervescent draughts, acids being slightly in excess of carbonates and bicarbonates with which these are prescribed.

Dilute Hypophosphorus Acid has an active negative ion, which forms a hypophosphite and is believed to be a general tonic. But it is so readily absorbed and excreted that no such action has been proved. Dilute Phosphoric Acid is also occasionally used for the same purpose. It is of some value in phosphaturia : the main action is acidification of urine which dissolves the precipitated phosphates.

ACTION ON GENERAL METABOLISM.—Acids are not absorbed as such but are neutralised in the duodenum by alkaline bicarbonates into sodium salt and circulate in the blood. CO₂ liberated stimulates the respiratory centre and is

(180) R

Acid. Hydrochlor. Dil. min. 15

Tinct. Nuc. Vom min. 10

Sp. Chlorof. min. 15

Inf. Gent. Co. ad. fl. oz. 1

After food, diluted with water

(181) R

Acid. Phosph. Dil. min. 15

Glycer. Pepsin. min. 60

Tinct. Limon. min. 20

Inf. Calumb. ad. fl. oz. 1

(182) R

Acid Sulph. Dil. min. 15

Tinct. Opii min. 5 to 10

Aq. Cinnam. Dest. ad. fl. oz. 1

For diarrhœa.

thrown out by the lungs. If taken internally for some time, the available blood alkalies are reduced especially the bicarbonates. The alkaline reserve of the blood is depleted threatening **acidosis**.

The kidneys excrete these rapidly in combination with ammonia retaining as much of the alkalies as possible: the urine becomes highly acid which during excretion, irritates the kidneys causing nephritis. If the alkaline reserve in blood is not sufficient to neutralise the acid, hæmoglobin of blood and ammonium carbonate, the precursor of urea are utilised. So urea is diminished and ammonia increased in the urine and the total nitrogen is also slightly increased. The pH of the blood is thus quickly made normal again. Death follows from acidosis if the quantity of acid taken is beyond the limit of compensation.

CO₂ in the tissues may be imperfectly removed and even a moderate exertion causes breathlessness.

As the blood plasma with its full alkaline reserve is better suited for the tissue metabolism, acids continued for a long time, in an otherwise healthy individual, tend to **diminish metabolism**.

The organic acids as acetic, lactic, citric and tartaric acids are oxidised in the body into carbonates which therefore behave as alkaline carbonates, causing **diaphoresis, diuresis, expectoration and purgation** by salt action. These are useful **antidotes** in caustic alkali poisoning.

Corrosive Acid Poisoning.—The antidotes are insoluble magnesia and magnesium carbonate or lime scraping from the walls and ceilings also chalk, followed by olive oil: stomach tube and emetics are not used.

SUMMARY—*Externally* Nitric and Trichloroacetic acids are used as **caustic**: dilute acetic and lactic acids are local astringents. *Internally*, hydrochloric acid is a digestant in hypoacidity. Citric and tartaric acids, oxidised into carbonates are slightly diaphoretic, diuretic, expectorant and laxative.

Non-official Preparations

ACIDUM SULPHURICUM DILUTUM.—Sulphuric acid 104 and distilled water to make 1000 (About 10% w/w). Dose, 5 to 60 minims or 0.3 in 4 ml.

ACIDUM SULPHURICUM AROMATICUM.—Sulphuric acid 70, tincture of ginger 250, spirit of cinnamon 15, alcohol (90%) to 1000.

Dose, 5 to 20 minims or 0.3 to 1.2 ml.

These are sometimes used along with tincture of opium (min. 10 of each) to control diarrhoea.

AMINOACETIC ACID also called *Glycine* (but not *Glycin* which is poisonous), is acetic acid with one of the hydrogen molecules replaced by the aminogroup. A white crystalline powder, readily soluble in water is given orally in 15 gr. doses twice daily in pseudo-hypertrophic muscular dystrophy and myasthenia gravis. In the latter condition, ephedrine hydrochloride, $\frac{1}{4}$ to $\frac{1}{2}$ gr. is also given 20 minutes after: in some cases, physostigmine 1/60 gr. is given hypodermically daily in addition.

Glycocoll 10% 10 c.c. intravenously daily for 10 days is recommended for angina pectoris: if good results are obtained, the injections are repeated with intervals of 10 days or more.

FORMIC ACID is an irritant resembling acetic acid. It is believed to be a muscle tonic increasing the muscular efficiency and restraining tremors: formates of sodium, potassium, calcium (Dose, 2 to 5 grs.) or of iron (Dose, 1 to 3 grs.) are sometimes given internally as general tonic but are of doubtful value.

LACTIGEN, LACTEOL.—Lactic acid bacilli in tablet form, are given with milk to help digestion. (Lactic acid bacilli curdle milk and are believed to inhibit the growth of other bacteria in the intestine. Such acid milk is easily digested).

NUCLEIC ACID, (Dose, $\frac{1}{2}$ to 2 grs.), NUCLEIN (Dose, 15 grs.) or SODIUM NUCLEINATE Solution (2 c.c. containing 0.1 gm.) hypodermically are given to increase the leucocytes in many infective conditions. SODIUM PENTOSE NUCLEOTIDE (Available as *Pentnucleotide*) in 7% solution, 10 to 20 c.c. is given intramuscularly, in agranulocytosis 4 times daily till the leucocytes definitely increase: then once daily till they are normal.

IV. IODIDES

The iodides usually used are of potassium and sodium with practically the same action. One time these were prescribed for many conditions but with the advance of pharmacology, in many cases these inevitably got out of use. These are still used in *tertiary syphilis*, *chronic bronchitis* and in certain *thyroid diseases*.

1. POTASSII IODIDUM (*Pot. Iod.*), Iodide of Potassium, KI.

Prepared by the action of an excess of iodine on a solution of caustic potash, evaporating to dryness, fusing with charcoal and purifying by crystallisation from water. Contains not less than 99% KI.

Colourless, transparent or white, opaque, cubic crystals or white granular powder, soluble at 15.5° in 0.7 of water, in 12 of alcohol (90%) and in 2 of glycerin.

It is an ingredient of *Liq. Iod. Aquos.*, *Liq. Iod. Fort.* and *Liq. Iod. Mit.*

Dose, 5 to 30 grains or 0.3 to 2 grammes.

2. SODII IODIDUM (*Sod. Iod.*), Iodide of Sodium, NaI.

Prepared in the same way as the above, using caustic soda instead. It is a white, inodorous, crystalline powder with a slightly saline taste: Contains at least 99% of NaI dried at 110°.

Soluble in less than 1 of water and 3 parts of alcohol (90%).

Dose, 5 to 30 grains or 0.3 to 2 grammes.

Incompatibles.—Acids, metallic salts, alkaloids, oxidising agents, bismuth subnitrate, liquorice and starch.

Pharmacology [and Therapeutics]

Iodides have no local action on the skin and are mostly used internally. Given orally in big doses, an iodide may cause slight irritation in the stomach from salt action, causing vomiting and rarely diarrhoea, more in some people than in others. But if given well diluted and in small doses in the beginning, tolerance is soon established.

ABSORPTION, DISTRIBUTION AND ELIMINATION.—It is rapidly absorbed unchanged from the intestine and appears in the circulation in a few minutes. This is so prompt that there is hardly much practical difference between an intravenous and oral administration.

It diffuses into nearly all extra-cellular fluid and is found in all natural secretions of the body and ultimately mostly excreted in the urine, about 60 to 80% being eliminated within 24 hours. It is found in saliva, tears, nasopharyngeal secretion, sweat, milk and sebum and to a less extent in the cerebro-spinal fluid. In smaller quantities, it is found in the lymphatic glands, lungs, liver and kidneys and in traces only in the nervous and fatty tissues. It has been found in the stomach as hydriodic acid which forms free iodine.

It is detected in the urine by adding a few drops of chlorine water and starch solution when blue colour appears.

In the process of excretion, it acts partly by salt-action and partly by the specific action of the iodide-ion. This excretion is much more quick than of a bromide. Iodide acts on the bronchial mucous membrane, increases the **bronchial secretion** and by diminishing the viscosity, facilitates its expectoration. [It is a common adjuvant to many cough mixtures¹⁸³⁻¹⁸⁴ in conditions of difficult and scanty expectoration especially in subacute or chronic bronchitis and asthma. Care should be taken to avoid iodides in pulmonary tuberculosis]. For the same reason, it is a mild **diuretic** also¹⁸⁵. But if continued fairly long, without any interval, this may lead to the atrophy of the mammae and testes, reducing the secretion of milk and sexual power. Sometimes it may cause skin eruptions in its excretion through the skin.

It tends to accumulate in less vascular **necrotic tissues** in greater concentration than in the healthy, since a dead tissue offers no resistance to diffusion of the salt. It therefore exhibits more powerful absorptive action on *gummatous deposits* (of tertiary syphilis) than elsewhere. In the same way, iodides are useful in *actinomycosis*, *sporotrichosis* and *blastomycosis*.

-
- | | |
|--------------------------|----------------------------|
| (183) R | Aq. Aneth. ad. fl. oz. 1 |
| Pot. Iod. gr. 2 | For bronchial asthma. |
| Ammon. Bicarb. gr. 3 | (185) S |
| Tinet. Scill. min. 10 | Pot. Iod. gr. 10 |
| Tinet. Seneg. min. 20 | Pot. Acet. gr. 15 |
| Syr. Tolu. min. 60 | Sp. Ammon. Aromat. min. 15 |
| Aq. Camph. ad. fl. oz. 1 | Liq. Ammon. Acet. |
| For chronic bronchitis. | Dil. min. 120 |
| (184) R | Tinet. Cardam. Co. |
| Pot. Iod. gr. 3 | Sp. Chlorof. aa. min. 15 |
| Pot. Brom. gr. 10 | Inf. Scopar. ad. fl. oz. 1 |
| Tinet. Strammon. min. 10 | For hydræmic nephritis. |
| Syr. Tolu. min. 60 | |

[This is frequently prescribed in 60 to 90 grains doses daily for the treatment of tertiary syphilis. It is not antisiphilitic but by dissolving gummatous tissues, makes the specifics more accessible to the parasites at the site of the disease. Therefore arsenobenzol preparations, bismuth or mercury¹⁸⁶ are also given at the same time. Aneurysm and other syphilitic diseases of the blood vessels are often benefited by progressively increasing doses of iodides].

Introduction of penicillin with beneficial effects in tertiary syphilis also, may replace iodides.

How the iodide acts is yet uncertain. One of the theories is that iodine is liberated by its decomposition. Coryza and skin eruptions sometimes follow the administration of iodides and resemble local irritation by iodine. But free iodine has not yet been definitely found in any of these places. As iodine readily combines with protein, it does not very much remain in the free state.

There is another theory also. An iodide given intravenously was thought to increase autolysis of the liver in animals and the serum did not inhibit trypsin. It is therefore possible that in a human being, it favours autolysis of the gumma by lowering the normal antitryptic activity of the blood serum.

Iodine applied locally, induces a certain amount of leucocytosis which is helpful in the absorption of chronic inflammatory products. So it is likely that when an iodide is given internally, it may have a similar **absorbent action** on deep-seated pathological tissues. With this hope, it is given in a large group of cases. [It is given in many kinds of chronic arthritis, neuralgias, chronically enlarged lymphatic glands and inflammatory exudates in the pleura and in the pericardium : also in actinomycosis. In many conditions of chronic inflammation, some benefit may follow].

An iodide supplies iodine necessary for the production of thyroxin. Children in a goitrous district, where food is deficient in iodine, are given iodised salt (0.001% of iodide with common salt) as a prophylactic. The dose of one-tenth milligram daily is usually sufficient. During pregnancy a small dose of iodide may be a prophylactic against deficiency. In **exophthalmic goitre** also, it is sometimes helpful : pathological hypersecretion of thyroxin is diminished and the general condition slowly improves. See p. 160.

It is used in the treatment of **thyroid deficiencies** e.g., endemic goitre and although helpful in some cases, in others

(186) E

Pot. Iod. gr. 5 to 30

Liq. Hydrarg. Perchlor. min. 30 to 60

Sp. Chlorof. min. 15

Inf. Quass. Rec. ad. fl. oz. 1

For tertiary syphilis.

there may be alarming symptoms of hyperthyroidism from over-production of thyroxin.

It is also used in **lead** and **mercury poisoning** and probably acts by forming soluble compounds with them, thus facilitating their excretion through the kidneys.

CIRCULATION.—In moderate doses, it has no effect on the circulation. But in cases of high blood pressure, it gives some relief probably by **relaxing the arterioles** and decreasing the peripheral resistance.

NERVOUS SYSTEM.—The iodine-ion has no specific action on the nerve tissues. It is however of some value in chronic neuralgias, some of which are probably syphilitic.

An old treatment of **leprosy** with iodide in increasing doses has not been sufficiently successful.

IODISM.—Certain toxic symptoms may appear during administration of an iodide. These are called **iodism**. This is probably due to the liberated iodine, acting as a local irritant or some alteration in the colloid equilibrium. The effects are more manifested on the upper *respiratory passages*, leading to swelling and increased secretion from the mucous membranes. The condition begins with a metallic taste in the *mouth*, running from the *nose*, cough and increased *pharyngeal and bronchial secretions* and slight difficulty in breathing rarely tonsillitis, pharyngitis, laryngitis, bronchitis and even oedema of the glottis. There is headache from congestion of the frontal sinuses and also conjunctivitis with oedema of the eyelids. During its excretion through the *skin*, eruptions of various types may sometimes appear : these are either localised erythema or papules becoming pustules and may resemble a primary skin disease.

It has been found that even a small dose may cause iodism as much as a bigger one. The tolerance varies in different persons and periodically so even in the same one. In fact, iodism is often a personal *idiosyncrasy* for reasons not quite known but often the tolerance is quickly established so that even a small starting dose can be rapidly increased to as much as thirty grains per dose, three times daily. The administration is to be kept up for some time as the drug is quickly eliminated by the kidneys.

Symptoms of iodism are easily controlled by stopping further administration of the drug and giving aromatic spirit of ammonia, min. 20 every 4 hours.

Organic preparations have the advantage of slow diffusion, slow liberation of iodide ion, slow excretion through the kidneys and are therefore likely to have more sustained action and less iodism. But the action is less certain.

Iodine preparations are **opaque to the X-rays**. So these are largely used in radiography. For the gall-bladder, Iodophthalein (orally) : for the lungs, Iodised oil or Lipiodol

(injected into the trachea); for the kidneys, Iodoxyl or Uroselectan-B and Diodone or Perabrodil (intravenously) and sodium iodide in 20% solution (introduced by a ureteric catheter into the pelvis of the kidney): for the female genital passages and the ventricles of the brain, Lipiodol (introduced directly) are frequently used.

SUMMARY.—An iodide taken orally diffuses readily to cause expectoration and diuresis. It is used as absorbent for chronic inflammatory deposits especially in tertiary syphilis, actinomycosis and in certain fungus diseases: in thyroid deficiency and in lead and mercury poisoning and certain organic preparations in skiagraphy. Inorganic salts may cause iodism.

Non-official Preparations

IODICIN (Ca-iodo-ricinoleic acid) in 3 grs. tablets 3 times daily.

IODIPIN (Iodine compound in sesame oil), 1 to 2 teaspoonful doses in emulsion (may also be given hypodermically).

IODALBIN, in 5 to 10 grs. doses is given 3 to 4 times daily for iodide action.

CALCIDIN¹⁸⁷ (Calcium iodide), in 2 to 4 grs. doses in aqueous solution and

SAJODIN¹⁸⁸ (Calcium iodobehenate), 5 to 15 grs. doses in powder are given for iodine action.

V. CALCIUM AND PHOSPHORUS

CALCIUM

1. **CALCI CARBONAS** (*Calc. Carb.*), Precipitated chalk, CaCO_3 .

Purified from the native form of calcium carbonate by *elutriation*. White or greyish white friable masses or a white powder with no smell or taste. It is insoluble in water and soluble with effervescence in dilute hydrochloric acid.

DOSE, 15 to 60 grains or 1 to 4 grammes.

It is an ingredient of *Hydrarg. c. Cret.*

OFFICIAL PREPARATIONS.—(i) **Pulvis Cretæ Aromaticus** (*Pulv. Cret. Aromat.*), See p. 53. **DOSE**, 10 to 60 grains or 0.6 to 4 grammes. (ii) **Pulvis Cretæ Aromaticus cum Opio** (*Pulv. Cret. Aromat. c. Opio*). See p. 53. **DOSE**, 10 to 60 grains or 0.6 to 4 grammes.

MISTURA CRETÆ, Chalk mixture (Not official).—Powdered chalk 6, tragacanth in powder $\frac{1}{2}$, refined sugar 3, cinnamon water 100.

2. **CRETA** (*Cret.*), Creta Præparata, Prepared chalk CaCO_3 .

Prepared by the interaction of a soluble calcium salt and a soluble carbonate. A white insoluble micro-crystalline powder without smell or taste: is insoluble or slightly soluble in water containing CO_2 . Contains not less than 98.5% of CaCO_3 dried at 100°.

DOSE, 15 to 60 grains or 1 to 4 grammes.

It is an ingredient of *Syr. Ferr. Phosph. Co.* and *Troch. Bism. Co.*

INCOMPATIBLES—Acids, phosphates, carbonates and sulphates.

(187) R

Calc. Iod. gr. 4

Syr. Aurant. min. 60

Aq. ad. fl. oz. 1

Mix. For subacute inflammation.

(188) R

Sajodin gr. 10

Lactosum gr. 5

Pulv. For bronchial asthma.

3. CALCI HYDROXIDUM (*Calc. Hydrox.*), Slaked lime, $\text{Ca}(\text{OH})_2$, *Chun.*

Prepared by the interaction of calcium oxide (lime) and water : a soft white powder with alkaline and slightly bitter taste. It should contain not less than 90% of $\text{Ca}(\text{OH})_2$. Soluble in 900 parts of water and by adding sugar, in 60 of cold water : strongly alkaline. It should be stocked in a well closed container.

INCOMPATIBLES.—Acid and metallic salts.

Liquor Calcii Hydroxidi (*Liq. Calc. Hydrox.*),—See p. 49. Lime water.

The clear fluid is then removed by syphoning (strength 0.15% w/v of $\text{Ca}(\text{OH})_2$).

DOSE, 1 to 4 fl. oz. or 30 to 120 ml.

4. CALX SODICA (*Calx. Sod.*), Soda lime is a mixture of the hard granules of calcium hydroxide and sodium or potassium hydroxide or both : absorbs not less than 20% of its weight of CO_2

White or greyish white granules or it may be coloured with an indicator which change when its absorptive power is exhausted. Partially soluble in water, completely soluble in dilute acetic acid.

5. CALCI CHLORIDUM (*Calc. Chlorid.*), Calcium chloride, CaCl_2 .

Prepared by neutralising hydrochloric acid with calcium carbonate and carefully evaporating and drying at a temperature never exceeding 200° . Contains not less than 98% of CaCl_2 (about 27% of Calcium).

Dry white granules or white deliquescent masses with warm, slightly bitter taste. Has great affinity for water and so should be kept well-corked. Soluble in $1\frac{1}{2}$ of water and in 3 of alcohol 90%.

DOSE, 10 to 30 grains or 0.6 to 2 grammes orally. When calcium chloride is prescribed for injection, twice the prescribed amount of hydrated calcium chloride shall be dispensed.

INCOMPATIBLES.—Carbonates, phosphates, sulphates and tartrates.

6. CALCI CHLORIDUM HYDRATUM (*Calc. Chlorid. Hydrat.*), Hydrated Calcium Chloride, $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$.

This is obtained by neutralising calcium carbonate with hydrochloric acid and crystallising the product. It contains between 93 and 102% of $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$. A 2.5% solution is isotonic. Colourless and odourless, very deliquescent crystals with a slightly bitter taste and soluble at 15.5° in 0.25 part of water and 0.95 part of alcohol (90%). The solution for injection is sterilised by heating in an autoclave or by filtration.

DOSE, 10 to 30 grains or 0.6 to 2 grammes intravenously.

It is an ingredient of *Inj. Sod. Chlor. Co.* and *Inj. Sod. Lact. Co.*

7. CALCI GLUCONAS (*Calc. Glucon.*), Calcium gluconate $[\text{CH}_2\text{OH}(\text{CHOH})_4\text{CO}_2]_2\text{Ca} \cdot \text{H}_2\text{O}$.

This is the normal calcium salt of gluconic acid, containing between 99 to 104% of $\text{C}_6\text{H}_{12}\text{O}_7 \cdot \text{Ca} \cdot \text{H}_2\text{O}$. A white odourless and tasteless crystalline or granular powder, soluble at 25° in 30 parts of water and in 5 of boiling water : insoluble in dehydrated alcohol, solvent ether and in chloroform. It contains about 9% of calcium.

DOSE, 15 to 60 grains or 1 to 4 grammes

Injectio Calcii Gluconatis (*Inj. Calc. Glucon.*), See p. 43. This is a supersaturated solution and if the crystals separate, this should not be used.

DOSE, 150 to 300 minims or 10 to 20 ml intravenously or intramuscularly.

8. CALCI LACTAS (*Calc. Lact.*), Calcium Lactate,
 $\text{CaC}_6\text{H}_{10}\text{O}_6 \cdot 5\text{H}_2\text{O}$.

A white and almost tasteless and nearly inodorous powder obtained by neutralising dilute lactic acid with calcium carbonate and evaporating: contains not less than 97% of $\text{C}_6\text{H}_{10}\text{O}_6\text{Ca} \cdot 5\text{H}_2\text{O}$. Soluble at 25°, 1 in 20 parts of water, readily soluble in hot water. A 4.25% solution is isotonic. It contains about 13% of calcium. It should be stocked in a well-closed container.

Dose, 15 to 60 grains or 1 to 4 grammes.

Tabellæ Calcii Lactatis (*Tab. Calc. Lact.*), See p. 56.

9. CALCI PHOSPHAS (*Calc. Phosph.*), Phosphate of lime,
 $\text{Ca}_3(\text{PO}_4)_2$.

Prepared by the interaction of calcium chloride and sodium phosphate in the presence of ammonia. White amorphous, inodorous and nearly tasteless powder insoluble in water. Contains not less than 85% of $\text{Ca}_3(\text{PO}_4)_2$.

Dose, 10 to 30 grains or 0.6 to 2 grammes.

SYRUPUS CALCI LACIOPHOSPHATIS, (Not official).—Calcium lactate 75, phosphoric acid strong 45, refined sugar 700, orange flower water 25 and distilled water to make 1000.

Dose, 20 to 60 minims or 2 to 4 ml.

Pharmacology [and Therapeutics]

Calcium salts are largely present in all living animals, in the *extracellular fluid* (but none in the cells), these being indispensable to all higher forms of life and for the activity of many ferments and for coagulation of blood. These salts make up the three fourth of the entire mineral contents of bones and teeth. The total calcium content of the human body is about 1,400 gm. (2% of the bodyweight) the bones and the teeth contributing about 99% as calcium phosphate. The blood serum contains about 10 mg. of calcium per 100 c.c. and in health this level is fairly constant being maintained by a balanced absorption and elimination. For this, the daily calcium requirement for an adult is about 0.8 gm. and for a growing child or a nursing mother, about 1 gm. Calcium exists in the blood in (a) *non-ionizable form* in combination with protein and probably as a supersaturated solution of calcium phosphate and carbonate and (b) from about 4.25 to 5.25 mg., in *ionizable form*. The latter only has active properties and maintains the stable and co-ordinated action of the different parts of the nervous system. The same is also responsible for proper bone formation, the failure of which in a growing child causes rickets and dental caries and in pregnant females osteomalacia.

In its absence again, milk is not curdled in the stomach by rennet and the coagulation of blood is retarded. The calcium-ion in the blood in the presence of thrombokinase, is essential for changing prothrombin into thrombin which acting on fibrinogen, coagulates blood. [Calcium is prescribed in various hæmorrhagic conditions and in urgent cases given intravenously, about 10 c.c. of calcium gluconate (10%)

solution being preferred. But in reality, in most of the hæmorrhagic conditions, the deficiency is of other elements and not of calcium]. Other ferments, as pepsin and trypsin, probably act without lime although it is not unlikely that for changing pepsinogen and trypsinogen to pepsin and trypsin, calcium is necessary.

The effect of the withdrawal of lime salts under experimental conditions is apparent when an isotonic solution of sodium chloride is perfused through an isolated frog's heart. It stops much earlier than when a minute trace of calcium is added to it. Irritability of the voluntary muscles and nerves is also maintained longer in a solution containing both sodium and calcium.

CALCIUM, SODIUM AND POTASSIUM BALANCE.—A frog's heart perfused with calcium chloride solution, the rate and strength of heart beat is increased with contraction of the blood vessels: a bigger dose stops the heart. With normal sodium chloride solution only, the heart soon stops in diastole. By adding a trace of calcium chloride to it, this at once resumes activity and the contractions are more prolonged with less relaxation. If now a minute quantity of potassium chloride is also added, these become more normal. A balanced salt solution (See p. 24:) is thus essential for normal muscular contraction.

In health, the proper muscular contraction of the heart muscles is the resultant of the activities of the three ions, sodium, potassium and calcium. The isolated tissues of mammals functionate best in a solution like Ringer-Locke solution containing NaCl 0.9%, KCl, 0.042%, CaCl_2 , 0.024% and NaHCO_3 0.02%. Glucose 0.1% is also needed to prevent tissue sugar from being washed out. (Clark).

The daily needs for calcium are satisfied by the little that is present in the food as in milk, yolk of eggs, meat and vegetables. A seer of cow's milk contains about 1 gm. of calcium, a full day's requirement in an easily assimilable form.

As the absorption of calcium is rather difficult, about 63% only being absorbed, the food should contain about 1 gramme of it daily. The blood calcium level is controlled by the supply of calcium in the food, stores already existing in the body especially in the bones, the reaction of tissues, vitamin D in the food and the supply of parathyroid hormone. The absorption and orderly utilization of Ca are regulated by fat and vitamin D. Its mobilisation from the stores already existing in the body into the blood and maintaining a steady level therein, is the function of the parathyroid hormone.

Both *acidosis* and *alkalosis* interfere with calcium balance. The former causes increased withdrawal of calcium from the bones and excretion; the latter lessens the ionized calcium in the blood causing increased nervous irritability. Chronic

diarrhœa and *renal insufficiency* interfere with adequate absorption of calcium.

If calcium-ion is in excess, as following an intravenous injection, the extra amount is quickly eliminated and a part is temporarily stored in the system to reach the normal level and no symptoms follow. If, however, it goes up to nearly the double of the normal limit and is maintained thereto, vomiting and diarrhœa start, even ending fatally.

TAKEN INTERNALLY by the mouth, calcium-ion is feebly absorbed; so a soluble salt of it as chloride is likely to cause catharsis by salt action but as a large part of it is precipitated in the alkaline solution of the intestine, it seldom does so. If the conditions noted above are fulfilled, calcium is absorbed from the upper part of the small intestine. There in the acid medium, soluble acid calcium phosphate is formed and absorbed or this takes place from a colloidal suspension. The remainder is precipitated as phosphate and carbonate in the lower portion of the small intestine.

An excess of either calcium or phosphate (the normal calcium/phosphorus ratio is 4 to 3) or increased alkalinity of the intestine favours precipitation of calcium in an insoluble and non-absorbable form. For the same reason, administration of hydrochloric acid favours absorption. Unabsorbed fat also precipitates Ca as insoluble soaps. What part Vitamin D plays is uncertain: probably it causes the gut contents to remain neutral. When vitamin D is deficient, these become unduly alkaline and calcium is precipitated. (Clark).

The bulk of the calcium absorbed is again excreted through the large intestine as phosphate or carbonate and a small quantity in the urine as chloride. If there is an excess of phosphate in the blood, it forms calcium phosphate and is excreted by the bowels. But if more chloride, it forms soluble calcium chloride which is excreted in the urine. Only a small quantity of it is therefore retained and this is usually sufficient to replenish the daily loss of calcium from the blood.

Excretion of the absorbed calcium by the bowels has recently been doubted. In a normal person after an intravenous injection of calcium gluconate and also in hyperparathyroidism and hyperthyroidism where blood calcium goes up, the urinary excretion of calcium increases but not of the faeces. So faecal calcium probably consists of unabsorbed portion of it only. (McCance and Widdowson in *Biochem. J.*, April, 1939).

Calcium chloride acts as a **mild diuretic** in some cases of subacute glomerulo-nephritis. Calcium chloride is made into insoluble carbonate or phosphate in the intestine, liberating chlorine. This combines with sodium in blood plasma reducing the blood alkalinity which tends to cause acidosis. Why acidosis should cause diuresis is not quite clear. Probably it lessens the amount of salts absorbed by the tissue protein. So the salts set free increase non-colloidal constituents of blood causing diuresis (Clark) by salt action.

Calcium salts are **constipating**, especially the carbonate which probably acts locally, by forming a bland coating over the

mucous membrane and thus by reducing the reflex excitability of the gut : may have direct sedative action on the neuromuscular mechanism also. [Calcium carbonate is therefore frequently prescribed in diarrhœa].

Ca-ion has some power to **retard transudation** as well as **inflammatory exudation** from finer arterioles [and is therefore useful in all kinds of anaphylactic phenomena associated with transudation into cellular spaces, as urticaria, angio-neurotic œdema, asthma and epidemic dropsy. It is also useful in the early stage of influenza, associated with profuse bronchial secretion and in œdema of the lungs].

In various **hæmorrhagic conditions**, different preparations of calcium are given by the mouth, intramuscularly or intravenously along with vitamin K preparations.

Calcium preparations are used for the prevention and treatment of **acute necrosis of the liver** as resulting from poisoning by chloroform, carbon tetrachloride and cinchophen : hydrated calcium chloride intravenously or calcium gluconate intramuscularly or intravenously are prescribed.

IONIC ACTION.—The specific action of the calcium-ion is not produced until it is given intravenously. A five per cent.



(Dixon)

Fig. 10.—The effects of K and Ca-ions on rabbit's heart. At A, Potassium chloride is added to the perfusion fluid and at B, Calcium chloride

solution of the chloride or 10% solution of gluconate is usually preferred. The injection especially of the chloride often gives an immediate sensation of warmth all over the body from immediate vaso-dilatation. The force and the frequency of the heart-beat are increased and the blood-vessels are contracted raising the blood pressure. The pupils are also contracted probably from direct action on the sphincter muscles. In large doses, the heart may be brought to a standstill and even 4 c.c. of 10 per cent. solution of chloride given rapidly is known to have done it.

An antagonism exists between the action of calcium and potassium on the heart. In the absence of calcium, potassium action prevails and the heart stops in diastole : with an excess of calcium, the heart stops in systole, "calcium rigor".

Electrocardiographic observation on an animal slowly perfused with calcium showed that in low concentration it is a direct cardiac stimulant but in high concentration, a depressant. When blood calcium reached about 29 mg.%, bradycardia probably vagal with change in T wave and when reached 60 mg.% cardiac arrest or ventricular fibrillation and death followed (Hoff & Winkler, 1939).

The high calcium level in blood stays only for a short time: a part is deposited temporarily in some unknown organ and is gradually used or excreted after the first excess is thrown out. The normal constant level is thus quickly restored.

There is some antagonism between the Ca. and Mg.-ions as the absorption of one increases the elimination of the other and the toxic action of Mg.-ion is relieved by Ca-ion given intravenously.

An optimum calcium concentration is necessary for the **uterine contractions**. When the ionized calcium level is lowered, the uterine activity is depressed and the organ becomes insensitive to oxytocic drugs and in the same way the activities of the oxytocic drugs may be potentiated by calcium.

NERVOUS SYSTEM.—A high blood calcium level has no marked effect. But a reduction of ionized calcium causes increased irritability of muscles of all varieties. This is not directly muscular, but due to hyperexcitability of the peripheral **motor nerve endings**. The **autonomic ganglion** cells are also stimulated (Bronk, 1939). Therapeutically, to maintain a co-ordinate nervous action, calcium preparations are given with parathyroid hormone in tetany and in various other spasmophilic conditions.

The clinical observations suggest that calcium ion has definite **antispasmodic action** on the smooth muscles. Slow intravenous administration has been found useful in relieving intestinal, biliary and renal colic.

The main therapeutic use of calcium is for ensuring **bone-formation**, [as in rickets and osteomalacia] and should be combined with Vitamin D and also Phosphorus.

Calcium has also some reputation as a **calcifying agent** in pulmonary tuberculosis and may be of value in primary complex (exudative stages) rather than in the later events.

Calcium salts have been found of value in **lead poisoning**. In chronic poisoning calcium and lead are deposited in the bones. At first calcium is depleted by low intake, administration of parathormone and ammonium chloride (causing acidosis); along with calcium, lead is also eliminated. This is followed by therapeutic administration of calcium and vitamin D to make up the loss.

Calcium Hydroxide

EXTERNALLY, it has the same action as other alkaline hydrates and is used as a mild **caustic**. In a weaker solution as lime water, it precipitates protein and is an **astringent**

[and is useful in many cases of weeping eczema¹⁸⁹⁻¹⁹⁰ and mixed with linseed oil or glycerin was used for burns]. On account of its cheapness, it is occasionally used to disinfect the stools of cholera and of typhoid fever.

INTERNALLY, lime water is given to children, one teaspoonful with 4 oz. of milk, to prevent formation of thick curds in the stomach. It is mildly **antacid** and **astringent** and checks vomiting and diarrhoea. It is an antidote to acid poisoning especially by oxalic acid: used as "milk of lime" shaken up with water forming a milky fluid.

Calx Sodica.—Soda lime is CO_2 absorbent and is used in the laboratory for removing CO_2 from chemicals. It is used for the same purpose in a closed circuit anæsthetic apparatus: one filling may go for 2 to 3 hours sufficient for one or two surgical operations. It is also used during determination of basal metabolic rate. An indicator changing colour when CO_2 saturation is obtained is usually incorporated.

The temperature rises but this should not exceed 40°C .

Calcium Carbonate

APPLIED EXTERNALLY, it has no special action: applied to a raw surface, it forms a bland coating and is sometimes made into dusting powders.

TAKEN INTERNALLY, it is mostly used for its **antacid** and **astringent** properties. Thus in hyperacidity of gastric ulcer, it is sometimes used with carbonate of magnesium and other carbonates. Suitable combination is creta and magnesium oxide, 15 grains of each: acid is more effectively neutralised and constipating action of one is corrected by the laxative properties of the other.

It controls diarrhoea¹⁹¹ especially of children with acid fermentation, by forming a bland coating on the mucous membrane of the intestine. [The aromatic chalk powders¹⁹² are frequently prescribed]. It is occasionally prescribed for the systemic action of calcium-ion. Unlike the chloride, the carbonate has no disagreeable local action on the stomach and being made into a soluble salt in the stomach, the rate of absorption from the small intestine is nearly the same as of other calcium preparations.

- (189) R
Calamina Preparata gr. 15
Zinc. Oxid. gr. 10
Liq. Calc. Hydrox. min. 90
Glycerinum min. 20
Aq. ad. fl. oz. 2

Lotion for weeping eczema.

- (190) R
Zinc. Oxid. gr. 60
Adeps gr. 240
Adeps Lan. gr. 60
Liq. Calc. Hydrox. fl. oz. 1
For irritating skin diseases.

- (191) R
Creta gr. 20
Mucil. Trag. q.s.
Tinct. Opii Camph. min. 30
Aq. Cinnam. ad. fl. oz. 1
For diarrhoea.

- (192) R
Pulv. Cret. Aromat. c. Opio
Bism Carb. aa. gr. 20
Pulv. For summer diarrhoea.

Calcium Chloride, Gluconate, Lactate and Laevulate

These are more commonly prescribed for calcium action and are given *by the mouth* and the first two by injections also. The chloride dissociates easily and coagulates protein even in dilute solution : therefore an intramuscular injection is painful and may cause tissue necrosis and in oral administration, unless well diluted, it is an irritant to the stomach and consequently gluconate and lactate (even better, calcium sodium lactate) are more popular : in fact, at present gluconate is more frequently used both orally and by injection than any other preparation. It is tasteless, nonirritating, readily absorbed and does not cause digestive disturbances. The gluconic acid residue is oxidised in the body. It is also more suitable for intramuscular and intravenous injections and a higher dose of it than of chloride as 5 to 10 c.c. of 10% solution may be given.

Orally these should better be given on the empty stomach¹⁹³ in combination with vitamin D and in this way, are more quickly absorbed.

Ca-ion has some protective action on the liver and is prescribed before the administration of carbon tetrachloride.

This specially by intravenous injection should not be given to a person already under full dose of digitalis, the action of Ca-ion resembling in some respects that of digitalis.

Calcium Phosphate

Calcium Phosphate (better still calcium hydrogen phosphate, $\text{CHPO}_4 \cdot 2\text{H}_2\text{O}$) with Cod-liver oil is given for **Calcium action** in rickets, a disease of children associated with defective bone formation. Vitamin D, present in the oil corrects the nutritional disorder. Syrup of Calcium lactophosphate is also prescribed for rickets, dental caries and tuberculosis.

The action of *phosphate-ion* within the tissue cells is the same as of chloride in the extracellular fluid, helping to maintain the acid-base balance by the kidneys : it is concerned in the bone formation along with calcium (p. 271) and is a component of enzyme systems, of carbohydrates, fats and other organic constituents of the body by forming phosphoric acid esters.

An adult requires about 1 gram. of inorganic phosphorus and this is wholly obtained from food : phosphate deficiency is practically unknown. (Cushny).

(193) R

Calc. Glucon. gr. 15

Liq. Calciferol. min. 10

Mucil. Acac. q.s.

Aq. Menth. Pip. ad. fl. oz. 1

For rickets.

Tribasic Calcium Phosphate¹⁹⁴ was given in gastroduodenal ulcer, mixed or alternating with tribasic magnesium phosphate in 30 to 60 grains dose instead of triple alkaline carbonates. These form a bland coating over the ulcer, stop hyper-secretion of the acid and favour healing.

Calcium phosphate is used in pharmacy as a bland vehicle.

SUMMARY.—The calcium-ion is essential for bone formation, blood coagulation, certain enzymic action and for co-ordinate action of the nerves and the muscles. *Therapeutically*, it is used with vitamin D and phosphorus for bone formation, in pathological exudative and transudative states, in tetany and other spasmophilic conditions also as antacid, local astringent, diuretic and antispasmodic. It is a preventive of hepatic necrosis and used in lead poisoning.

Non-official Preparations

CALCIUM LEVULATE.—The calcium content is relatively high being 14.8% (gluconate is 9%), more soluble in water (so may be dispensed in a mixture) and may be given intramuscularly and intravenously in 15% solution. It has thus several advantages.

DICALCIUM PHOSPHATE, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, contains 4 of Ca and 3 of P fulfilling Ca-P ratio suggested by Mellanby.

DOSE, 15 to 20 grs. (available as tablet or powder). This with vitamin D, makes *Calfo-rayol* capsules.

CALCIBRONAT, calcium brom-lactobionate, in $7\frac{1}{2}$ to 15 grs. doses orally or 5 to 10 c.c. ampoules intramuscularly is prescribed as nerve sedative.

ALCALZIUM, CALDEFERRUM: Calcium gluconate with vitamin D and iron in tablet. Two tablets 2 to 3 times daily.

DUSART'S SYRUP, mainly calcium lactophosph. in the syrup given to rickety children in half to one tea-spoonful doses.

CALCI SULPHAS EXSICCATUS, Calcium sulphate $\text{CaSO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ (IND. PHARM. LIST), in dried state in sealed tin, makes plaster of Paris splints: 2 pounds in a pint of water makes it set rapidly and firmly. Sod. chlorid. 1% added hastens setting. Plaster of Paris splint is now the method of choice for fixing up a bone or joint either for fracture or for tubercular disease.

PHOSPHORUS

In minute doses, it is a general *metabolic stimulant*. In growing children, pronounced effect is produced on *bone-formation*. But it is absorbed with difficulty being insoluble in water and in body fluid and is not now therapeutically used.

HYPOPHOSPHITES AND GLYCEROPHOSPHATES.—These are more frequently prescribed than phosphorus itself.

The preparations in common use are Calcium hypophosphite (Dose, 3 to 10 grs.). Iron hypophosphite (Dose, 1 to 5 grs.). Potassium hypophosphite (Dose, 1 to 6 grs.) and Sodium glycerophosphite (Dose, 3 to 10 grs.).

The Hypophosphites are readily absorbed but are almost wholly excreted in the urine unchanged. There is no definite evidence that these are at all oxidised or utilised in the system in any way.

(194) B

Calc. Phosph.

Mag. Phosph. aa. gr. 30

Pulv. One in the morning, after 3 afternoon feeds and after the last feed at night. (Hurst).

The Glycerophosphates are rapidly broken down into phosphates and glycerin. The phosphate is mostly excreted in the urine and glycerin is oxidised. There is no definite evidence in their favour either that these are of any substantial value. Glycerophosphates are prepared by the hydrolysis of lecithin, an important constituent of the nerve tissue. So it was hoped that a part of these may be synthetised into lecithin in the body and act as nerve tonic. These are frequently prescribed in a condition of general debility and malnutrition as in tuberculosis or rickets and in nervous exhaustion and in these they have some clinical reputation^{195, 199}.

Radio Phosphorus.—This isotope of phosphorus P^{32} (p. 12), given orally or better intravenously in 0.5 to 2 millicuries doses weekly for 4 to 8 weeks causes internal radiation especially in the leukæmic cells of chronic leukæmia and in polycythæmia vera and is giving favourable clinical results.

VI. VITAMINS

The vitamins or accessory food factors are certain apparently indifferent substances, required in small quantities to maintain normal health although of no substantial food value as a source of energy.

The need for fresh food including vegetables for maintaining normal health was considered essential from pre-historic days. The first positive evidence of such a need was realised when in the 16th century the sailors had to go out on long voyages for several month depending on dry stored food only. Two diseases became the outstanding feature in them: one was scurvy and the other, beri-beri. It was found out as early as 1600 A.D. that lemon juice was a preventive for the former and later in 1885 Tabaki found that by lessening rice and adding more meat and barley to the diet the latter also could be prevented.

Modern researches in vitamins really started by Hopkins in 1912. Funk introduced the word "vitamine" which was subsequently changed to vitamin. Recently chemical formulæ have been found including methods of manufacture by synthesis.

- (195) B
Calc. Hypophosph. gr. 5
Liq. Calc. Hydrox. min. 60
Aq. Camp. ad. fl. oz. 1

A general tonic.

- (196) B
Calc. Hypophosph. gr. 6
Tinct. Quass. min. 30
Sp. Chlorof. min. 15
Aq. Aneth ad. fl. oz. 1

A general tonic.

- (197) B
Syr. Hypophosph. Co.
Containing many hypophosph. salts, (Ca, K, Na, Fe, Mn.) with quinine and strychnine. Dose, 1 to 2 tea-spoonfuls.

Fellow's Syrup and *Grimault's Syrup* are similar preparations.

- (198) B
Syr. Glycerophosph. Co. Dose, 1 to 2 tea-spoonfuls.

This is a combination of many glycerophosph. (Na, K, Ca, Mn, Fe) with strychnine and caffeine.

This is available in the form of syrup as *Ner Vigor*, *Tonic-Glycerophosphate* and also made into tablets.

- (199) B
Sanatogen (Casein combined with sodium glycerophosph.).

One to two tea-spoonfuls are added to one cupful of hot milk.

It has been realised that in commercial storage, the vitamins may be wholly or partly destroyed by oxidation. A human being is solely dependent on food for the supply of his vitamins which are obtained from vegetables directly or from egg or flesh of animals or from milk. The storage, mode of preparation and the quantity available in the food are essential items to maintain the optimum vitamin level.

The absence of a vitamin in a food is determined by certain *signs of disease* appearing in the experimental animal when put on to it for some time and subsequently *cure* of the disease when the missing vitamin is added. The signs of deficiency appear if (i) the food has not the necessary amount of one or several of the vitamins, (ii) if the need for these is increased as in a woman during pregnancy and lactation and in a growing child, also (iii) when on account of disturbances in the digestive system, these are not sufficiently absorbed.

Several of these are *soluble in fat* as vitamins A, D, E, and K. These are stored in the body and the deficiency takes some time to produce symptoms. The others are *water soluble* as vitamins B complex, C and P. These are not stored as much and least probably is vitamin B complex. Its deficiency thus causes symptoms early.

In deficient fat absorption as in obstructive jaundice, fat soluble vitamins are not absorbed. This soon causes hæmorrhagic tendency and certain ocular disturbances. Chronic bowel infection and even gastritis cause polyneuritis and other signs of deficiency from diminished absorption of vitamin B₁.

FAT-SOLUBLE VITAMINS

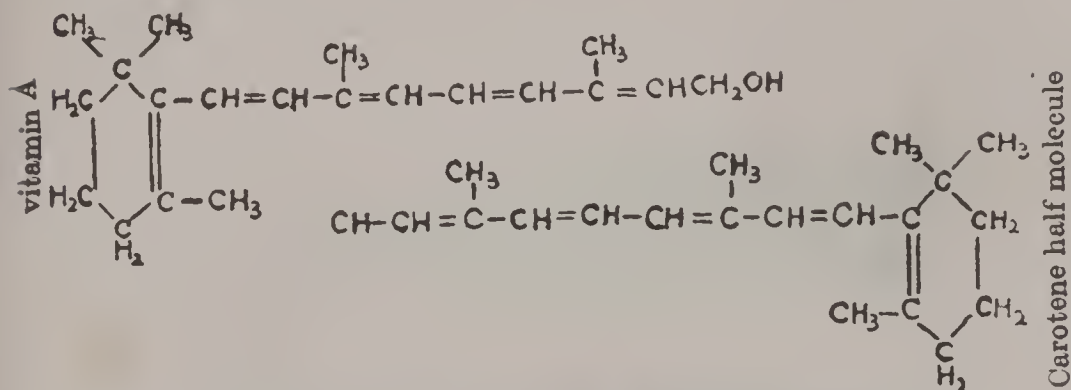
There are four Vitamins A, D, E and K ; one time A and D were regarded as one substance and E and K have recently been introduced.

VITAMIN A

The yellow plant pigment *carotene*, C₄₀H₅₆, which is a hydrocarbon and occurs in 3 forms as alpha, beta (this is twice as powerful) and gamma carotene, is transformed in the animal body into colourless vitamin A, (C₂₀H₂₉OH) which is an easily oxidisable alcohol with five double bonds. Carotene and another yellow pigment, *cryptoxanthin*, present in yellow maize, are capable of this transformation and are thus the precursors of vitamin A (Provitamin A).

Carotene is largely present in green leaves and growing shoots but is not identical with chlorophyll ; in these, carotene is only covered by the green colour. Vitamin A is also present in liver, liver oils (especially of fish) also in yolk of eggs, butter and milk

of green grass fed cows. In a normal animal, it is obtained from plants as carotene and transformed by carotenase in the liver into vitamin A : by being taken up by Kupffer's cells it is stored in the liver also to a less extent, in the kidneys and the lungs. The natural sources for a human being are green vegetables, milk and eggs.



One Beta-carotene molecule breaks down into 2 molecules of vitamin A : $C_{40}H_{56} + 2H_2O = 2C_{20}H_{28}OH$

It is comparatively stable and stands cooking fairly well. With higher rise of temperature, it is slowly destroyed.

For therapeutic purpose, it is obtained from fish liver oil or synthetically ; of the former the best source is halibut oil and codliver oil is fairly good : sharkliver oil is also a source. Several Indian fish liver oils both of salt and fresh water have this vitamin : one obtained from the latter (fresh water fish) is called vitamin A₂.

One unit of vitamin A is 0.6 microgram of the international standard or of β -carotene. A preparation is assayed by a special diet given to a rat or chemically, antimony trichloride giving a blue colour.

Liquor Vitamini A Concentratus (*Liq. Vitamin. A Conc.*).—A concentrated solution of vitamin A contains in 1 grm. 50,000 units of vitamin A activity. It may be a fish liver oil, a blend of fish-liver oils or prepared by dissolving at a temperature not exceeding 60°, a source of vitamin A in a suitable vegetable oil as arachis oil.

A pale yellow or yellow oily liquid with a faint (not rancid) odour and bland or slightly fishy taste. The activity is determined by comparing with the standard preparation and expressed in units per gramme.

Dose, 1 to 10 minims or 0.06 to 0.6 ml., approximately 2500 to 25,000 units of vitamin A.

Pharmacology [and Therapeutics]

Vitamin A being fat soluble, an adult animal has a good reserve of it and takes several months to show symptoms of deficiency. A young animal has a poorer store and shows it earlier. Carotene given with a fatty meal is well absorbed but given with liquid paraffin, absorption is poor as vitamin A is soluble in paraffin and gets fixed in it.

Vitamin A maintains the integrity and development of epithelial tissues. The deficiency signs are therefore (a) in connection with **epithelial cells** : (b) also with **vision**, vitamin A being required for synthetising the visual purple : this lacking, vision in dim light is lost.

(i) The symptoms start with lessening of sebaceous secretions with a tendency to keratinization of the superficial layers of the *skin* shown by dryness of the skin with papular eruptions.



Fig. 11

Fig. 12

(P. D. & Co.)
Fig. 11-12. Papular eruptions on the arm and buttock
as a result of vitamin A deficiency

(ii) *Growth* : this is retarded.

(iii) *Eye changes* are imperfect accommodation in dim light, afterwards night blindness :

Other eye affections are formation of epithelial plaques on the conjunctiva (Bitot's spots), xerosis or dryness of the conjunctiva and cornea (xerophthalmia) and keratomalacia, eyes being light sensitive on account of a type of purulent ophthalmia ; finally loss of sight.

(iv) Keratinization of the superficial epithelia increases liability to recurrent respiratory and bowel infections and puerperal sepsis.

(v) Defective formation of enamel-making cells of the teeth and injury to the gums cause pyorrhoea alveolaris and formation of renal calculi are also sometimes attributed to this deficiency.

An adult healthy human being requires about 3000 units and a growing child or a nursing mother, 6000 units of vitamin A daily. In deficiency, the dose should be 30,000 units or more daily till an improvement is obvious. An overdose has no marked toxicity. Vitamin A is readily absorbed from the alimentary tract reaching maximum concentration in 5 to 8 hours: only in severe cases, a parenteral administration is indicated. Excepting what is lost by oxidation and excreted in milk, it is stored in the liver which is thus a storehouse when this intake is deficient. [The main therapeutic uses are for night blindness, keratomalacia, relapsing bronchitis, broncho-pneumonia, certain types of bowel diseases, senile vaginitis, rheumatoid arthritis and occasionally for subacute combined degeneration]. Milk, eggs, green vegetables, cod liver, halibut-liver or shark liver oil or concentrated proprietary preparations are the source.

SUMMARY.—The main actions are two: (i) it has an important role in vision and (ii) essential for the integrity of the epithelial cells of the skin, certain mucous membranes and of glands.

COMMERCIAL PREPARATIONS.—*Gelseals Alphalin* (Pills containing vitamin A, 10,000, 25,000 and 50,000 units). *Prepalin*, capsulo of 24,000 units: liquid 72,000 units per c.c. and ampoule each 100,000 units of vitamin A for injection. *Vitarel A* has 33,000 units per capsule, *Aroleum* liquid has 30,000 units per g. and 4500 units per capsule.

INDIAN PHARMACOPCEIAL LIST PREPARATIONS

OLEUM SELACHOIDEI, Shark Liver Oil contains in one gram. not less than 10,000 international units of vitamin A activity.

Dose, 3 to 15 min. or 0.2 to 1 ml. (vitamin A, 1500 to 7500 units).

Extractum Malti cum Oleo Selachoides.—Shark liver oil 50 g. and malt extract 950 g.

Dose, 60 to 240 min. or 4 to 16 ul.

CALCIFEROL, Vitamin D, $C_{28}H_{44}OH$

This may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent. The product after removal of the solvent is dissolved in alcohol (95%) or other suitable organic solvent and strongly cooled. The separated unchanged ergosterol is removed by filtration and the solvent is removed by evaporation. The residue is dissolved and by special chemical treatment CALCIFEROL is crystallised from it. The crystals are colourless, inodorous and tasteless: insoluble in water but is soluble in fats and oils. It is fairly stable and capable of prolonged storage also. One milligram of it contains 40,000 units of antirachitic activity (vitamin D) or one unit is 0.025 microgram or gamma.

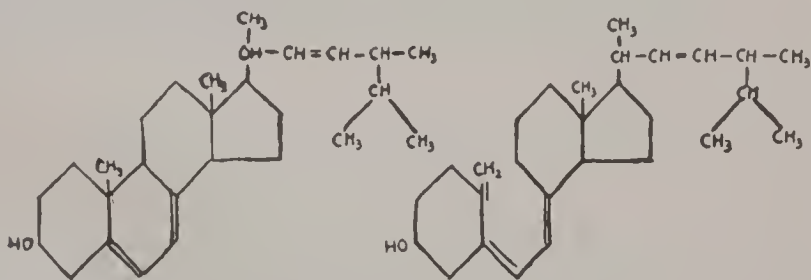
Chemically, the parent substance is œstrane $C_{28}H_{48}$, a combination of a cyclopentene and a phenanthrene ring. Ergosterol has three double bonds, two in the ring systems and one in the side chain. (Dixon).

Dose, 1/2400 to 1/600 grain or 0.025 to 0.1 milligram (1000 to 4000 units) daily, *prophylactic*; 1/1200 to 1/120 grain or 0.05 to 0.5 milligram (2000 to 20,000 units) daily *therapeutic* for an infant or adult.

OFFICIAL PREPARATIONS.—(i) **Liquor Calciferolis** (*Liq. Calciferol.*), Prepared by warming to 40° a 1% suspension of Calciferol in a suitable vegetable oil such as arachis oil, CO_2 being bubbled through it to facilitate solution. The quantity of oil is so adjusted that 1 mil. contains about 3000 units of *Antirachitic Activity* (vitamin D). Dose, 5 to 20 minims or 0.3 to 1.2 ml. (1000 to 4000 units) *prophylactic* and 10 to 100 minims or 0.6 to 6 ml. (2000 to 20,000 units) *therapeutic*, daily for an infant or adult. (ii) **Liquor Vitamini D Concentratus** (*Liq. Vitamin. D Conc.*), Concentrated solution of vitamin D contains i. l. grm. 10,000 units of antirachitic activity consisting of a suitable fish-liver or a blend of fish-liver oil or a solution of a source of vitamin D made at a temperature not exceeding 60° in a suitable vegetable oil such as arachis oil. Source of vitamin D may be calciferol, a fish oil rich in vitamin D or a preparation from fish-liver oil by extraction, partial saponification or distillation: a pale yellow oil with a faint (not rancid) odour and bland or slightly fishy taste. Dose, 1½ to 6 minims or 0.1 to 0.4 ml. : approximately 1000 to 4000 units, daily *prophylactic* : 3 to 30 minims or 0.2 to 2 ml. (2000 to 20,000 units) daily, *therapeutic*.

Pharmacology [and Therapeutics]

The nonsaponifiable fraction of the oil, the animal sterol, *Cholesterol* and the vegetable sterol, *Phytosterol* present in various animal and vegetable products, subjected to ultraviolet radiation, produce vitamin D. It has now been found that this property is not of cholesterol itself but of an impurity in it called *Ergosterol*. This sterol was originally isolated by Tanret (1889) from ergot and hence the name. A similar sterol or one closely allied to it has been obtained from a wide range of lower plants, especially from yeast. All these on irradiation yield vitamin D. In fact, vitamin D contents of a large number of food-stuff may be considerably augmented by irradiation. Leafy vegetables however do not contain much vitamin D.

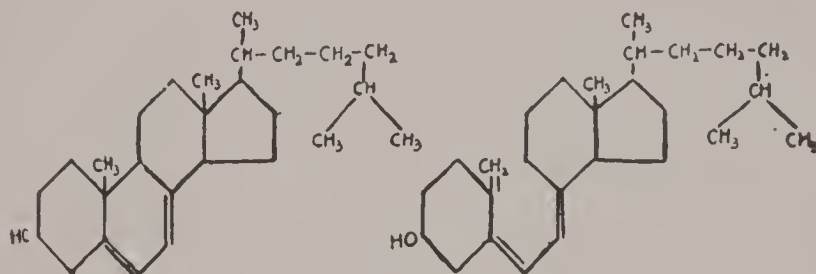


Ergosterol by irradiation to changed Calciferol (vitamin D₂)

Bourdillon (1930) first isolated it in crystalline form and called it *calciferol*. Irradiated ergosterol or calciferol, vitamin D₂, is the constituent of commercial vitamin preparations and is obtained from vegetable source.

About ten pro-vitamins D have been recognised : of these one is ergosterol and the other 7-dehydrocholesterol ; on irradiation, the former makes vitamin D₂ and latter, vitamin D₃.

The human skin also contains a sterol and this, exposed to sun's rays or ultra-violet rays, produce vitamin D₃.



7-dehydrocholesterol, by irradiation changed to vitamin D₃

Vitamin D₃ is naturally present in fish-liver oil (especially of cod and halibut), in egg-yolk and to a less extent, in butter.

Vitamin D₁ was the name given to lumisterol calciferol-mixture and not pure calciferol. Vitamin D₄ is dehydrocalciferol.

Ultraviolet exposure or sunbath to the skin and the administration of codliver oil were known to be helpful in curing rickets. In calciferol, the curative factor is obtained in concentrated and standardised form, and is now largely used in practice. The advantage is that in a small bulk in readily absorbable form, a bigger dose of the vitamin can be administered which is not possible either with usual food-stuff or with cod-liver oil. Calciferol can be given by intramuscular injection also.

In the absence of vitamin D, calcium and phosphorus, necessary for **bone formation**, are not absorbed in balanced proportion to be deposited in the osteogenetic tissue. But the exact mechanism is still uncertain. Vitamin D appears to be mainly concerned in the intestinal absorption of calcium and phosphorus : also probably converts organic phosphate to inorganic phosphate in the bone (Cohn and Greenberg, 1939).

Three items Ca, P and vitamin D are, however, essential for orderly growth of the skeleton. (See p. 271).

A growing child, a pregnant woman and a nursing mother require an adequate supply of vitamin D. If this is deficient, the bones and teeth of the child are badly formed, resulting in *rickets* and *dental caries* and in a pregnant woman, *osteomalacia*. Administration of vitamin D in such conditions has both preventive and curative effects.

Although may be absorbed from the skin when rubbed with a fatty basis or injected subcutaneously or intravenously, it is best administered by the mouth. It is stored to a moderate extent and excreted in the milk. For absorption, presence of

bile (probably desoxycholic acid) in the intestine is essential : chronic diarrhoea interferes with absorption.

The maintenance dose for an infant or a pregnant or nursing woman is about 700 international units : for curing rickets, a bigger dose is necessary 5000 international units and in refractory cases, 20,000 to 50,000 units daily. Blood calcium should be estimated weekly.

Recently, calciferol has been found useful in *lupus vulgaris* : either 600,000 international units 3 times weekly by injection or 150,000 units in tablet 3 times daily orally are given : injection method gives better result.

But administered in big doses or if continued fairly long even in a moderate dose, it causes *overcalcification* at the growing ends of the bones. An excessive dose may so raise the blood calcium level that some of it may be deposited in the kidneys as calcium phosphate stone : deposits have also been described in the blood vessels, heart, bronchi and stomach. In children the first symptom of overdose is loss of appetite followed by vomiting and diarrhoea with loss of weight which indicates that the dose should be reduced. Such an event is not likely with ingestion of vitamin D containing food, but may result from concentrated impure medicinal products.

SUMMARY.—The main action is to promote intestinal absorption of calcium and phosphorus to maintain the necessary blood concentration of these for adequate bone formation : deficiency causes rickets or osteomalacia. An excess causes hypercalcification : prepared by irradiation of ergosterol (vitamin D₂).

Dihydrotachysterol (A. T. 10) prepared by irradiating ergosterol, related to Vitamin D₂, has action like that of parathyroid hormone and is used for raising the blood calcium level in *hypoparathyroidism* especially in post-operative tetany : it is only slightly antirachitic. Dose, 5 to 15 mg. daily till the blood calcium reaches normal : this takes about a week or ten days.

Non-official Preparations

CHOLESTEROL, in 5 to 15 grs. doses 3 to 4 times daily, is given in Black-water fever : believed to be anti-hæmolytic.

From this are derived or allied to this are *vitamin D* and *calciferol*, *sex hormones*, *corticosterone*, *evocators* regulating normal growth, *carcinogenic agents* and *aglycones* of digitalis glucosides. (Clark).

OLEUM MORRHUÆ (Ol. Morr.), Cod-liver Oil.

The oil is obtained from the fresh liver of the Cod, *Gadus morrhua* and other species of *Gadus*, from the coasts of Norway, and from this solid fat has been separated by filtration at about 0°C. It is a pale yellow oil with a fishy smell. It should be kept in a well filled and well closed bottle away from light.

It contains (i) *Olein* (85%) which is oleate of glyceryl and is a fluid fixed oil. (ii) *Palmitin*, *myristin* and *stearin* (10%); (iii) The corresponding *fatty acids*, oleic, palmitic and stearic. (iv) Minute quantities of

iodine, bromine, cholesterin, bile salts, sulphuric and phosphoric acids. (v) Trimethylamine. It contains in one gramme not less than 600 units of vitamin A and 85 units of vitamin D.

Dose, 60 to 180 minims or 4 to 12 ml., daily given in divided doses.

(i) **Emulsio Olei Morrhuæ** (*Emuls. Ol. Morrh.*), See p. 38. Dose. 120 to 360 minims or 8 to 24 ml. Given in divided doses.

(ii) **Extractum Malti cum Oleo Morrhuæ** (*Ext. Malt. c. Ol. Morrh.*), Contains approx. 15% of Cod-liver Oil. See p. 40. Dose, 60 minims to 1 fl. ounce or 4 to 30 ml, daily in divided doses.

OTHER VITAMIN A AND D PRODUCTS

1. **Liquor Vitaminorum A et D Concentratus** (*Liq. Vitamin. A et D Conc.*).—Concentrated solution of Vitamin A and D contains in 1 gm. 50,000 units of vitamin A and 5000 units of vitamin D. It may consist of a suitable fish-liver oil, blend of fish-liver oils or prepared by dissolving at temperature not exceeding 60°, a source of each of vitamin A and D in a suitable vegetable oil as oil of arachis. A pale yellow oily liquid with a faint (not rancid) odour and bland or slightly fishy taste. Slightly soluble in alcohol 95%.

Should be kept in a well-closed container, protected from light.

Dose, 1 to 10 minims or 0.06 to 0.6 ml. approximately vitamin A 2500 to 25,000 units and vitamin D 250 to 2500 units daily.

2. **Oleum Hippoglossi** (*Ol. Hippogloss.*) is a fixed oil extracted from fresh or suitably preserved liver of halibut, *Hippoglossus*. A pale yellow or golden yellow liquid with fishy odour and taste. This contains in each gramme not less than 30,000 units of vitamin A activity. The vitamin D activity varies : usually between 2500 to 3500 units per gramme.

Dose, 1 to 8 minims or 0.06 to 0.5 ml., approximately vitamin A 1500 to 12,000 units, daily.

Pharmacology [and Therapeutics]

Cod-liver Oil differs from other fixed oils in containing a large amount of unsaturated fatty acids. All fixed oils and fats must be desaturated first in the liver before these are available for combustion : cod-liver oil, being already desaturated, is more readily oxidised than any other oil. It emulsifies more quickly and is easily digested and absorbed. It also contains a small amount of cholesterol and a minute quantity of iodine (0.03%).

All these combined, make it an ideal food for many wasting diseases²⁰⁰⁻²⁰¹. The general nutrition quickly improves and the body-weight steadily goes up. [So it is a time-honoured and favourite medicine for tuberculosis and malnutrition in general].

It contains, in addition, two fat soluble vitamins, vitamins A and D (probably D₃). These are present in the unsaponifiable lipoid present in it. The vitamin A enhances the bodily growth, maintains a healthy condition of the conjunctiva and

(200) B

Calc. Hypophosph. gr. 5
Ol. Morrh. min. 60
Mucil. Acac. and Trag. q.s.
Syr. Tolu. min. 60
Aq. Cinnam. ad. fl. oz. 1
One 3 times daily after food.

(201) B

Ferr. et. Ammon. Cit. gr. 15
Ol. Morrh. min. 60
Mucil. Acac. q.s.
Ol. Limon min. 1
Aq. Chlorof. ad. fl. oz. 1
One 3 times daily after food.

the skin, prevents night blindness and is probably anti-infective also. The vitamin D helps the absorption of calcium and phosphorus and prevents and cures rickets, a disease of children associated with general malnutrition and defective bone formation. Although cod liver oil is quite efficient to cure, vitamin D concentrates (as calciferol) are more popular: in the latter form, the vitamin may be given in much bigger doses, in more agreeable and absorbable form in a small bulk.

Vitamin D of crystalline calciferol is not exactly the same as of cod-liver or halibut liver oil: the latter is not crystallisable and the therapeutic efficiency of the two is also not the same, an infant reacting better with calciferol. In fact, vitamin D factor has apparently several antirachitic sub-groups of graded potency. Halibut liver oil has a higher proportion of the vitamin A but its vitamin D content is variable.

The source of vitamins in cod and halibut is still uncertain. Probably vitamin A is derived from green algæ and diatoms in the upper waters of the ocean eaten by small fish which ultimately serves as food of the cod and vitamin D is synthesised in its body and stocked in the liver.

Direct sunlight and ultra-violet rays increase the vitamin D content of cod or halibut liver oil.

[Cod-liver oil frequently prescribed in many conditions of malnutrition either to supply a readily assimilable fat or for vitamins A and D. As the vitamins are now available separately in stable, standardised and concentrated form, cod-liver oil is getting less popular.

If the plain oil cannot be taken for the nauseous smell, any of the various emulsified or malted preparations, cod-liver oil concentrates or the alcoholic extracts are prescribed].

Cod-liver oil has been used as a **surgical dressing** in burns, many septic sores also in exfoliative dermatitis.

SUMMARY.—Cod-liver oil is an easily assimilable nourishing food and a source of vitamins A and D₃.

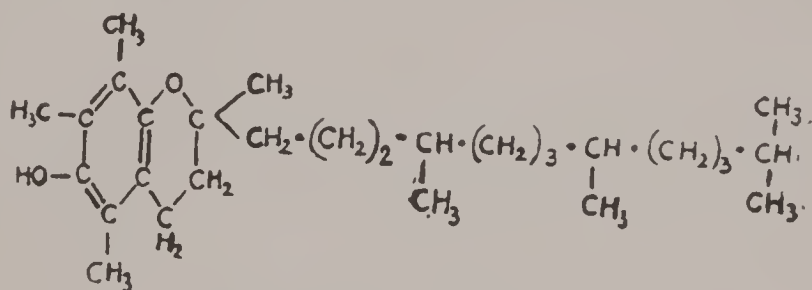
On account of unsettled condition in Norwegian waters, the supply of cod-liver oil has been diminished. Halibut liver oil is a potent substitute. Some of the Indian salt and fresh water fish also have these vitamins in the liver. In the place of cod-liver oil, for the vitamins only, the *concentrates* or the unsaponifiable portion of cod-liver oil dissolved in a vegetable oil or calciferol D₂ and vitamin D₃ may be used.

COMMERCIAL PREPARATIONS.—Halibut liver oil containing vitamin A and D is available as *Holiverol* or *Halibutol*, DOSE, 2 to 10 min. twice daily. Other standardised preparations are, *Adexolin*, *Vigantol*, *Vogan*, *Viosterol*, *Navitol*, *Super D Concentrate*, *Alphadattalin*, *Irradol*, *Ostelin*, *Radiosterin* and *Radiostol*, DOSE, 5 to 15 min. daily. *Ostelin Forte*, a tablet contains 50,000 units and 1 c.c. ampoule 600,000 units of calciferol. *Dekadexolin* has in 1 c.c. vitamin A 60,000 and vitamin D 10,000 units in oil. *Radiostoleum Conc.* has vitamin A 75,000 and vitamin D 15,000 units in 1 c.c. These are for injection. **SHARK LIVER OIL** contains about 16,500 units of vitamin A and 40 units of vitamin D per gram.

SODIUM MORRHUATE (Not official).—Given intravenously into a vein in 5% solution, it causes destruction of the intima, followed by *sclerotic obliteration*. This is sometimes used in varicose veins and occasionally in piles. The solution is a local irritant and care should be taken to prevent any escape into the subcutaneous tissue.

VITAMIN E (Not-official)

This is a fat-soluble vitamin largely present in the wheat germ oil from wheat embryo also in oats, lettuce leaves and other growing green leaves and in germinating seeds. It is to a less extent present in animal tissues also as in muscles, fat and viscera. It has recently been synthesised : it is a higher alcohol, $C_{22}H_{40}O_2$ and called dl- α -tocopherol. Beta and gamma tocopherols also have some but less vitamin E activity. It is fairly resistant to heat, light, air, also to acids and alkalies at normal temperature and is insoluble in water.



Alpha-tocopherol, vitamin E

The absence of vitamin E is said to cause sterility : in the males, there is loss of seminiferous epithelium and in the females, conception is followed by death and resorption of the developing embryo (Evans, 1922). Wheat germ oil or α -tocopherol has been therapeutically given to females, for sterility and tendency to abortion without obvious cause. The results are encouraging. This vitamin is probably necessary for the normal activities of the anterior pituitary (maintaining oestrogen balance) also to prevent pregnancy toxæmia.

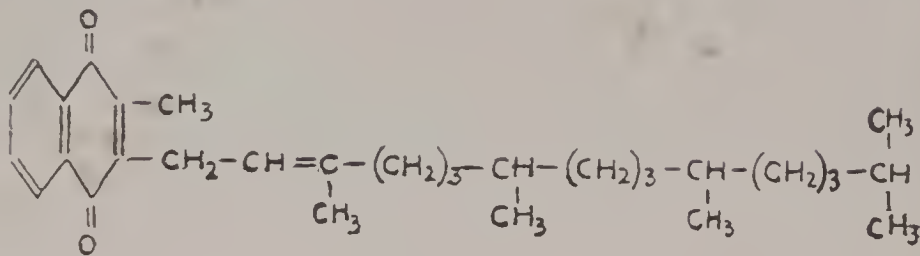
This has also been used in *degenerative nervous diseases* as amyotrophic lateral sclerosis and *muscular dystrophy* : 25 mg. t.i.d. for active treatment and 10 mg. as the maintenance dose. More recently it is used in *collagenosis* (lupus erythematosus, scleroderma, dermatomyositis and others) in dose not less than 200 mg. daily. *Thromboangiitis obliterans*, *Raynaud's disease* and *coronary insufficiency* are treated for causing capillary dilatation with α -tocopherol acetate 75 mg. and Priscoline 20 mg. orally 4 times daily. The natural product is thought to be better than the synthetic one.

COMMERCIAL PREPARATIONS.—Wheat germ oil Lilly, one to 2 teaspoonful. Viteolin capsules (6 mg.), Gelseal Eprolin (50 mg.) : Ephynal (3 mg., 10 mg. and 25 mg. tablets). Tocopherex (50 mg. capsules) : Fertitol (3 mg. capsules) and Phytoferol (6 and 30 mg. capsules) are used : smaller doses are as prophylactic against abortion and bigger doses for muscular dystrophies.

VITAMIN K

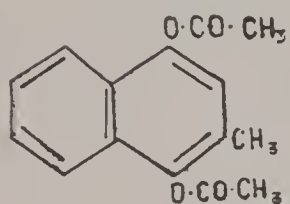
This is also called "Koagulation" vitamin and is fat soluble. This is obtained naturally from vegetables as alfalfa, spinach, carrot tops tomatoes and soya bean oil and is in non-saponifying, nonsterol fraction of hog liver fat. Putrefied protein as

fish meal and casein is a good source. This vitamin has been prepared *synthetically* also.



Vitamin K₁

1. ACETOMENAPHTHONUM (*Acetomenaphthon.*), C₁₅H₁₄O₄.



Acetomenaphthon is 1 : 4-diacetoxy-2-methylnaphthelene, prepared by reducing 2-methyl 1 : 4-naphthaquinone with zinc and acetic acid in the presence of acetic anhydride.

A white crystalline powder, inodorous or has slight odour of acetic acid, almost insoluble in water, slightly soluble in cold alcohol (95%), soluble in 3.3 of boiling alcohol (95%) and in acetic acid.

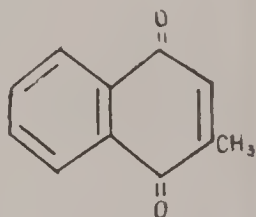
Dose, 1/30 to 1/6 grain or 2 to 10 mg.

Tabellæ Acetomenaphthoni (*Tab. Acetomenaphthon.*), See p. 56. Contains 89 to 110% of C₁₅H₁₄O₄.

Dose, as of Acetomenaphthone : 10 mg. tablets are usually supplied.

2. MENAPHTHONUM (*Menaphthon.*), C₁₁H₈O₂.

Menaphthone is 2-methyl-1 : 4-naphthaquinone prepared by oxidising 2-methylnaphthalene, containing not less than 98.5% of C₁₁H₈O₂, calculated with reference to the substance dried over sulphuric acid in a vacuum desiccator.



A bright yellow crystalline powder with a characteristic odour : irritating to the skin and the mucous membrane : changes to light brown on exposure to sunlight (decomposition) : this should be stored protected from light. Insoluble in water, slightly soluble in alcohol (95%) and soluble in 50 parts of fixed oils.

Dose, 1/60 to 1/12 grain or 1 to 5 mg. by intramuscular injection.

Injectio Menaphthoni (*Inj. Menaphthon.*), See p. 44.

Pharmacology [and Therapeutics]

Dam of Copenhagen in 1935 found that animals fed on food deficient in certain fat-soluble fractions suffer from spontaneous bleeding with fall in prothrombin contents and delayed coagulation. This fraction he named vitamin K : one obtained from vegetable source is K₁ and from animal source, as putrefied protein is K₂.

It was found that 1,4-Naphthoquinone had vitamin K activity. This activity is considerably increased by adding a methyl group. This compound, called *Menadione*, is 3 times as active as the natural vitamins K₁ or K₂ and, being synthetically prepared, is better standardised and is obtainable in large quantity at a small cost. Dissolved in oil, it is suitable for intramuscular injection. Acetomenaphthon in tablet is used

for oral administration. Recently water-soluble preparations suitable for intravenous injection also are available.

The natural source is what available from food in vegetable oils and formed in the intestinal tract by bacteria. In the absence of bile in the intestine, this vitamin along with other fat-soluble vitamins is not absorbed and is responsible for diminished formation of prothrombin. Deficiency of prothrombin (hypoprothrombinæmia) in blood delays coagulation of blood. Healthy state of the liver is also essential. In **hæmorrhagic state** with diminished prothrombin and no gross liver disease, vitamin K is of great value.

In *obstructive jaundice* and *biliary fistula* causing hæmorrhages and in hæmorrhagic disease of the new-born, this is of special value. The usual dose is 10 mg. orally. In jaundice, administration of bile salt about 2 g. orally is also necessary to ensure absorption of the fat-soluble vitamin from the intestine. If rapid action is desired, menaphthone is given intramuscularly in 0.2% solution or a water-soluble preparation intravenously.

Urticaria resistant to other treatment may be benefited by vitamin K products, (acetomenaphthone 10 mg. daily).

It is of *prophylactic value* in a pregnant woman in the later months of pregnancy both for the mother and the infant: it is of value before a severe surgical operation 10 mg. of vitamin K with 2 g. of bile salt are given daily orally.

SUMMARY.—Vitamin K and its synthetic homologues increase the **prothrombin contents** of the blood and is used in many hæmorrhagic states orally or parenterally.

COMMERCIAL PREPARATIONS.—An oily solution, KAPILIN or PROKAYVIT (Menaphthone) 1 c.c. containing 5 mg. is used intramuscularly. PROKAYVIT ORAL (Acetomenaphthone 10 mg. tablets orally): KAPILIN water-soluble and SYNKAVIT (menophthone diphosphoric ester) also water-soluble: 10 mg. oral tablets (calcium salt) or 10 mg. ampoules (sodium salt) for injection, are used and effective. SYNKAMEN (Amino-methylnaphthol) 1 mg. in 1 c.c. given i.m. or i.v. in 1 to 5 mg. dose.

WATER-SOLUBLE VITAMINS

The water-soluble vitamins are at present 3 in number. The vitamin B Complex and Vitamin C are official. Vitamin P more recently introduced, is not yet official.

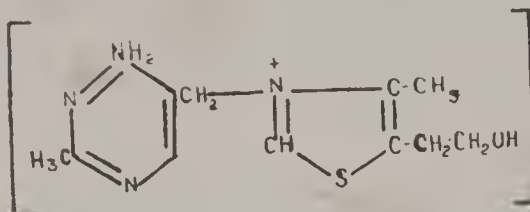
VITAMIN B COMPLEX

The present conception of vitamins as a food factor commenced from the study of this vitamin first obtained from rice polishings by Funk (1911). It has now been found that in vitamin B complex, a number of vitamins are included some of which have been isolated from natural sources and also prepared synthetically. These are thiamine, riboflavin, nicotinic acid and nicotinamide, pyridoxine, pantothenic acid, biotin, para-aminobenzoic acid, inositol, choline, folic acid,

vitamin Bc and also probably vitamins B₁₀ and B₁₁. Recently B₁₂ has been isolated.

1. ANEURINÆ HYDROCHLORIDUM (*Aneurin. Hydrochlor.*), Thiamine Hydrochloride, C₁₂H₁₇ON₄SCl, H₂O.

Aneurine chloride hydrochloride, vitamin B₁ or thiamine hydrochloride is 3(4'-amino-2'-methylpyrimidyl-5'-methyl-4-methyl-5-Beta hydroxyethylthiazolium chloride hydrochloride, obtained from rice polishings, yeast and other natural sources or by synthesis.



It contains between 20.4 to 21.2% of total Cl: between 10.3 to 10.8%

of Cl as hydrochloride and between 95 to 103% of anhydrous aneurine hydrochloride.

Colourless monoclinic plates often in rosettes with faint and branlike odour and bitter taste. It is stable if faintly acid and rapidly deteriorates in neutral and alkaline solution.

Dose, 1/60 to 1/20 grain or 1 to 3 mg. prophylactic and 1/6 to 1/2 grain or 10 to 30 mg. therapeutic, daily.

OFFICIAL PREPARATIONS.—(i) *Injectio Aneurinæ Hydrochloridi* (*Inj. Aneurin. Hydrochlor.*), Sec p. 42. Dose as of Aneurine hydrochloride. If strength is not stated, 25 mg. in 1 ml. should be served. (ii) *Tabellæ Aneurinæ Hydrochloridi* (*Tab. Aneurin. Hydrochlor.*), Sec p. 56. Contains 85.5 to 119% of C₁₂H₁₇ON₄SCl. Dose as of Aneurine hydrochloride. If the quantity is not stated, 1 mg. tablets are supplied.

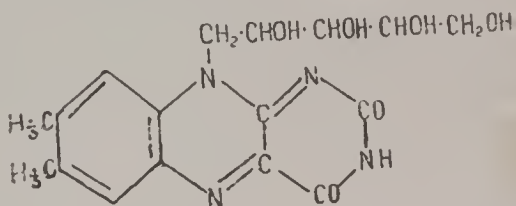
2. RIBOFLAVINA (*Riboflav.*), Riboflavine, C₁₇H₂₀O₆N₄.

Riboflavine or Lactoflavin is 6:7-dimethyl 9-(d-1'ribityl) iso-alloxazine. It may be obtained from yeast, green leaves, milk and other natural sources or by synthesis.

It contains not less than 14.5% and not more than 15.2% of nitrogen, calculated on a substance dried over sulphuric acid for 18 hours.

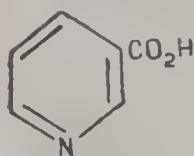
An orange yellow crystalline powder, with slight odour and slightly bitter taste. Slightly soluble in water, more so in physiological saline solution and in dilute alkali hydroxide solution, slightly soluble in alcohol but insoluble in solvent ether and in chloroform. It should be stored protected from light especially if in solution.

Dose, 1/60 to 1/16 grain or 1 to 4 mg. prophylactic and 1/12 to 1/6 grain or 5 to 10 mg. therapeutic daily.

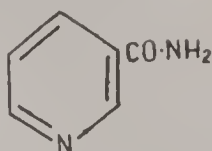


3. ACIDUM NICOTINICUM (*Acid. Nicotin.*), Niacin.

Nicotinic Acid, C₆H₄NCOOH is pyridine-3-carboxylic acid and may be obtained from nicotine by a suitable oxidising agent: contains not less than 99.5% of C₆H₄O₂N. Natural sources are liver, kidney, pork flesh and yeast.



Nicotinic Acid



Nicotinamide

Inodorous white crystals or crystalline powder with feebly acid taste. Soluble in 75 parts of water at 15°, readily in boiling water and boiling alcohol 95% or in alkaline solution.

Dose, 1/3 to 1/2 gr. or 15 to 30 mg. prophylactic and 3/4 to 4 gr. or 50 to 250 mg. therapeutic daily.

Tabellæ Acidi Nicotinici (*Tab. Acid. Nicotin.*), See p. 56. Strength is 83.5 to 110% of nicotinic acid.

Dose, as of Nicotinic acid.

4. NICOTINAMIDUM (*Nicotinamid.*), $C_6H_6ON_2$.

This is nicotinic acid amide (pyridine-3-carboxylic acid amide), prepared by thionyl chloride acting on nicotinic acid and treatment of the result with ammonia. It contains not less than 98.5% of $C_6H_6ON_2$ in a sample desiccated in vacuum for 18 hours.

A white crystalline powder almost inodorous with a bitter taste. Soluble in 1 of water, about 1.5 of alcohol (95 %), 10 of glycerin at 25° and sparingly in solvent ether. This should be kept in a well corked container.

Dose, $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 15 to 30 mg. *prophylactic* and $\frac{3}{4}$ to 1 gr. or 50 to 250 mg. *therapeutic* daily.

Tabellæ Nicotinamidi (*Tab. Nicotinamid.*), tablets of Nicotinic Acid. See p. 57. Strength is 88 to 110% of nicotinamide.

Dose, as of Nicotinamide.

Pharmacology [and Therapeutics]

Vitamin B_1 or Aneurine, $C_{12}H_{16}N_4OS$, is comparatively unstable and stands boiling for a short time being readily destroyed by oxygen in alkaline solution. In acid or neutral solution, this is not so readily destroyed and in the dry state, it is more stable. Vitamin B_2 is more heat-resistant so that if yeast is autoclaved, B_1 is destroyed but B_2 remains. This complex vitamin is present in the yeast, germinating seeds, whole cereals, green vegetables, tomatoes, milk, liver of animals and in eggs. Given orally it is absorbed mainly from the small intestine: there is evidence that bacterial activity synthesises this vitamin in the intestine and this is absorbed from the large intestine. Before utilisation, aneurine is phosphorylated (this occurring in all nucleated cells especially in the liver, kidneys and white blood cells). It is not, however, sufficiently stored in the tissue and consequently the symptoms of deficiency appear early.

1. ANEURINE, THIAMINE.

Aneurine is readily absorbed into the circulation reaching highest concentration in the liver, heart, brain, and the kidneys. It is also found in the voluntary muscles, spleen and the lung. The quantity present at a time depends on the previous store and the dose taken. About 5 to 10% is destroyed in the body and the excess is excreted in urine. Severe diarrhoea retards absorption.

A diet, deficient in aneurine in a young animal, causes **malnutrition** and retarded growth. But more important is **polyneuritis** in an adult. A pigeon on deficient diet, soon loses appetite and bodily vigour. It loses strength and is constipated which causes intestinal toxæmia: this has been found to be due to atrophy of the intestine and its atony. In about three weeks, nervous symptoms appear as weakness of

the legs and convulsive attacks ending fatally. Temperature falls by 10 to 12°F. Blood shows an increase in blood sugar (lowered glucose tolerance) and has pyruvic and lactic acids indicating **carbohydrate metabolism** disturbance. Vitamin B₁ aneurine, being converted in the body into its pyrophosphate (co-carboxylase), takes part in an enzyme system essential for the catabolism of carbohydrate. During utilisation of glucose in the system, an intermediate product pyruvic acid is formed and for its oxidation and decarboxylation, aneurine is necessary. If this is deficient, pyruvic and lactic acids accumulate in the tissues, glucose is not readily absorbed from the intestine and strength and energy of the individual progressively fail.

The minimum aneurine requirement of an adult is about 1 mg. with optimal intake of 3 mg. and of a child, 0.5 mg. This increases in pregnancy, lactation, hyperthyroidism, febrile condition and in fact in any condition causing increased metabolism. If placed on a deficient diet, the distinctive features of the deficiency appear. It has been found that an individual kept on a diet 50% of normal aneurine requirements, within five days showed fatigue, lassitude, loss of appetite, gastro-intestinal disturbance, palpitation, precordial pain, dyspnoea on exertion, burning sensation in feet and cutaneous hyperæsthesia (Jolliffe, 1939).

If the deficiency is greater, signs of neuritis, myocardial weakness, intestinal atony and sometimes skin œdema appear as is seen in beri-beri. The symptoms however, disappear fairly quickly when a food rich in this vitamin is supplied.

[Vitamin B₁ is now available in pure form and has been found of distinct value in **beri-beri**, a type of polyneuritis in which this vitamin deficiency is an important factor: the dose is 20 to 50 mg. daily. It is also of value in various kinds of **neuralgia** and **neuritis**, especially in sciatica, (usually 3 to 5 mg. of the standard product available as tablet, 2 to 3 times daily orally or/and intramuscularly also: in a severe case 25 to 100 mg. daily): is used in certain types of anorexia and retarded growth in young children. It is necessary in moderate doses during pregnancy and lactation, in infection and in hyperthyroidism especially of long duration. It is also necessary in **diabetes mellitus**: it helps carbohydrate metabolism along with insulin and is a preventive of polyneuritis. It is an excellent tonic during convalescence after prolonged illness as after typhoid fever in combination with nux vomica and dilute alcohol. It is useful in atonic **constipation**. It is also helpful in certain types of **œdema**: best given intramuscularly in 50 mg. dose daily].

When sulphonamide intestinal antiseptics are given for several days, the bacteria synthesising this vitamin in the intestine being much reduced in number, a vitamin B preparation should also be given.

Bigger doses may cause toxic symptoms and metabolic disturbances especially signs of deficiency of other vitamins of vitamin B group, more often in an ill nourished person.

SUMMARY.—Aneurine is of value in **peripheral neuritis** and cardiac disturbances especially of beri-beri: also helps **carbohydrate metabolism** and certain types of **œdema**.

COMMERCIAL PREPARATIONS.—*Benerva* (3 and 5 mg. tablets and 50 and 100 mg. per c.c. rubber-capped phials): *Betalin S* (5, 10, 12, 15, 25 and 50 mg. tablets: 30, 50, 60 and 100 mg. per c.c. phials): *Bedome* (3, 10, 25 and 100 mg. tablets and 50 and 100 mg. per c.c. phials): *Berin* (1, 3, 5 and 10 mg. tablets and 25, 60 and 100 mg. per c.c. phials): *Vibex* (1, 3, 5 and 10 mg. tablets and 20, 50 and 100 mg. per c.c. phials): *Thiamine hydrochloride* (3 and 5 mg. tablets and 60 and 100 mg. per c.c. phials).

2. RIBOFLAVIN, LACTOFLAVIN, Vitamin G, $C_{17}H_{20}N_4O_6$.

Flavin is a water-soluble pigment originally isolated from skimmed milk (Blyth, 1879). Liver and kidneys are its richest source and the heart muscles contain this more than the skeletal muscles. Yeast, malted barley, young growing leaves, egg and milk are good sources.

Lactoflavin appears to be concerned with the oxidation reduction reaction of the cells, yellow oxidation enzyme

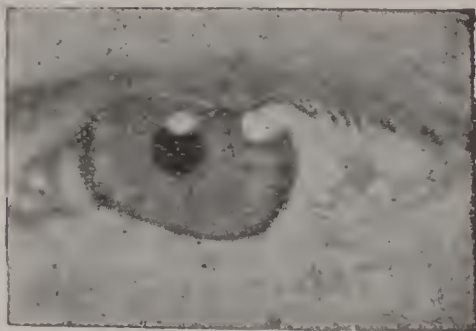
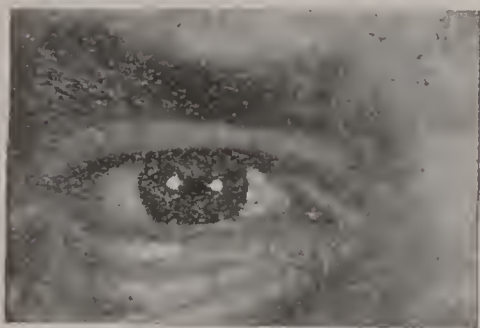


Fig. 13.—Rosacea Keratitis

Fig. 14.—Conjunctivitis and Scleritis
Riboflavin deficiency signs

carrying oxygen to the tissues (cell respiration) and is consequently **growth promoting**. It is a constituent of amino-acid oxidase and xanthene oxidase and also other basic enzymes. For these activities, riboflavin is first phosphorylated in the intestine, liver and the blood cells. Riboflavin is present in every tissue of the body and is associated with intracellular catalytic processes. One unit represents 3 to 5 microgrammes of the substance.

The normal adult requirement is about 3 mg. per day and for a child 1 mg.

The signs of deficiency (ariboflavinosis), in a human being appear in 3 to 4 months. Pallor and subsequent ulceration at the angles of the **mouth** (angular stomatitis, cheilosis): magenta coloured **tongue** with papillæ flattened and hypertrophied: a mild erythema associated with a fine desquamation of the **skin** of the forehead and face and in more advanced stages, seborrhœa of the nasolabial fold (Sebrell and Butler, 1938) and

roughening of the skin of the mouth and nose also **ocular disturbances** as photophobia, congestion of the sclera, hypervascularisation of the cornea (rosacea keratitis) leading to corneal opacity and impairment of vision (Kruse, 1940, are seen.

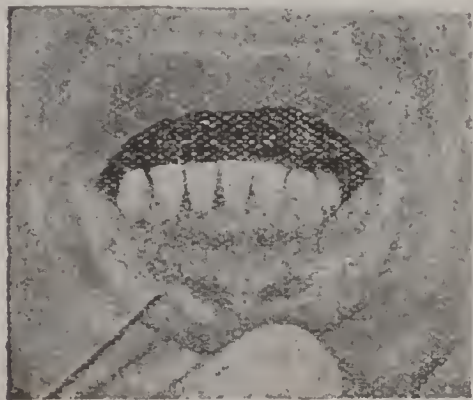


Fig. 15.—Lips ulcerated

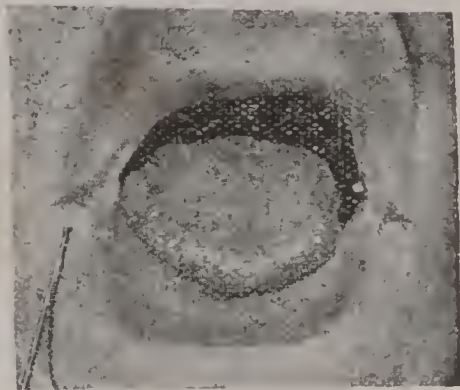


Fig. 16.—Angular stomatitis

Certain amount of Nicotinic Acid deficiency is also present

With these, a certain amount of muscular weakness, in-co-ordination, burning sensation of the feet and paræsthesia may be present. A growing child fails to grow.

Clinical Application.—(1) Riboflavin is the true cure for the pathological conditions described in the lips, tongue, skin and the eyes. Doses are ten to 15 mg. daily orally or and intramuscularly. (2) It is of some value in pellagra. A pellagrin not fully improving with nicotinic acid, often shows much progress with 50 mg. doses of it daily for 2 or 3 days: clinically, aneurine, riboflavin and nicotinic acid deficiencies are often combined. (3) It is also sometimes given in chronic intestinal disturbances with diminished absorption of fat and anæmia in 5 to 10 mg. doses daily orally or better parenterally.

Riboflavin is destroyed slowly in the body. It is not much stored and if an excess is given, it is mostly excreted in the urine.

SUMMARY.—Ariboflavinosis causes lesions in the **mouth, tongue and the skin**: also **ocular disturbances**.

Tablets *Riboflavin* 1 mg., 5 mg. and as *Beflavin* 10 mg.: also ampoules 10 mg. are available.

3. NICOTINIC ACID (Niacin or P.P. Factor) and NICOTINAMIDE.

The amide is probably an essential part of certain cellular co-enzymes which promote cellular oxidation and hence useful in nutrition. Daily requirement is probably 15 to 20 mg. Its main sources are liver, kidneys, pork flesh and yeast. It is readily absorbed from the alimentary canal and about 30 to 50% is excreted in the urine.

Nicotinic acid has an important function in **carbohydrate metabolism**. Nicotinamide is present in diphosphopyridine

nucleotide (co-enzyme I) and in triphosphopyridine nucleotide (co-enzyme II), the carbohydrate enzymes. It potentiates the action of insulin and is helpful in diabetes mellitus especially if neuritis is present. It is of some value in **encephalopathy** of alcoholic addicts and ulcerative conditions in the mouth and throat and in radiation sickness. In a severe case about 1 g. daily may be given.

A rat on a diet deficient in this pellagra-preventive component, shows retarded growth, loss of appetite and a fall of temperature. Later, lesion in the skin and the mucous membranes of the mouth and tongue appear.

Nicotinic acid has been found of great value in the human disease of pellagra. In this disease, *skin* (characteristic dermatitis), *mucous membrane* (especially glossitis and stomatitis) and the *brain* (lassitude, mental torpor and emotional instability) symptoms are present. Daily dose is 150 to 500 mg. (available in 50 mg. tablets) given orally or partly by intramuscular injection also (50 mg. ampoules) in severe cases. The improvement is rapid : hence this vitamin is called P. P. (**pellagra preventing**) factor. Sometimes other members of vitamin B complex are also necessary to complete the cure, especially riboflavin for ulcerations of the lips.

In some cases of oral administration of less soluble sulphonamides, bacterial synthesis of nicotinic acid in the intestine is interfered with. So in case of prolonged treatment with sulphonamide, nicotinic acid has also to be given.

Nicotinic acid given intravenously (but not the amide) causes temporary **vaso-dilatation** especially of the blush area with a rise in skin temperature and itching. These disappear in two hours. But oral administration does not cause much symptoms. So for intravenous administration, nicotinamide is preferred. Intravenous injection of nicotinic acid, 5 to 10 mg. has been given in coronary thrombosis and angina pectoris to cause vasodilatation. In status anginosus, 100 mg. in 500 c.c. of normal saline is given very slowly intravenously. It is sometimes helpful in intermittent claudication and Meniere's disease.

SUMMARY.—Nicotinic Acid and nicotinamide are **pellagra preventing** and helpful for **carbohydrate metabolism**. Nicotinic Acid is in addition, a **vaso-dilator**.

TRIETHANOLAMINE OF NIACIN, 3% solution commencing from 5 c.c. increased to 20 or 30 c.c. intravenously daily has been found useful in obliterating endarteritis : about 20 injections make a course.

4. **PYRIDOXINE**, Vitamin B₆.—This is chemically 2-methyl-3 hydroxy-4, 5-hydroxymethyl pyridine and used as hydrochloride. Gyorgy found that rats on controlled diet developed dermatitis and acrodynia which was cured by yeast. Harris and Folkers (1939) prepared it synthetically and used on the human being in pellagra. Cases not fully cured with nicotinic acid, riboflavin and thiamine, improve readily with 50 mg. of

synthetic pyridoxine especially when insomnia, irritability, muscular weakness and inability to walk persisted. The mechanism of action is unknown. It has also been found useful in vomiting of pregnancy and radiation, in certain types of anæmia, and in agranulocytosis, also in muscular dystrophy and parkinsonism; 50 to 100 mg. intramuscularly and in less severe cases, orally may do.

The natural sources are seeds of cereal grains, legumes, rice polishings, yeast, liver, egg yolk, meat and fish.

Hexa-Betalin and *Benadon* (vitamin B₆) are available in 25 mg. tablets and 50 mg. per c.c. sterile solution for injection.

5. **PANTOTHENIC ACID.**—The function of pantothenic acid in the human being is unknown. Daily excretion is about 3 to 4 mg. Yeast, peanuts, whole wheat, liver and eggs are good sources. Calcium Pantothenate is used with other members of vitamin B complex in *multiple deficiency*. It is also used in premature greying of the hair and *alopecia*. Dose is 150 mg. or more daily.

6. **BIOTIN.**—The chief sources are yeast, liver, eggs, peas and cereals along with other members of vitamin B complex. Daily requirement of a human being is estimated to be about 150 μ g. It is an essential growth factor for many bacteria and moulds: also necessary for the growth of yeast in culture: the signs of deficiency in a human being are believed to be a scaly dermatitis, pallor of the skin, atrophy of the papillæ of the tongue and disturbed red cell formation.

7. **PARA-AMINOBENZOIC ACID.**—This is present in yeast and liver extract. Its function in the human body is still uncertain. It was used in the treatment of *Rickettsia* infection before chloromycetin and aureomycin came into use.

8. **INOSITOL.**—This is found in plants as phytin (calcium magnesium phosphoric acid combination). It is an essential factor in a vitamin B complex food. It is found in animal tissues, vegetables and fruits. No deficiency state in the human being has been described.

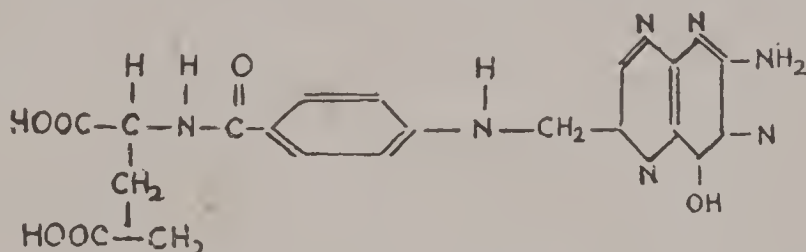
9. **CHOLINE**, a constituent of lecithin is also a member of vitamin B complex. Its deficiency in the mammals cause fatty degeneration of the liver and kidneys and is used in hepatic cirrhosis and paralytic ileus.

Available as TABLETS V.L. *Pantothenic Acid*, *Pabavel* (para-aminobenzoic acid), *Inositol* and *choline chloride*.

10. **FOLIC ACID.**—This member of vitamin B complex has recently attracted much attention. The name *folic acid* is given because the substance was isolated from spinach. It is also obtained from green leaves of other plants, yeast and from liver and kidneys. Folic acid variants are called (a) *vitamin M* (deficiency causes pellagrous symptoms in monkeys), (b) *vitamin Bc* (deficiency causing nutritional anæmia in monkeys), (c) *vitamin B₁₀* and *vitamin B₁₁* causing growth and feather develop-

ment in chicks) and (d) the "eluate factor" from liver and (e) *L. casei* factor (essential for the growth of *Loctobacillus casei* and *Str. lactis R*) Folic acid is also prepared *synthetically* (Angier and Boothe, 1945), called pteroylglutamic acid (P.G.A.). This is a bright yellow microcrystalline powder, inodorous and tasteless, sparingly soluble in water. Therapeutically, this is as effective as the natural product.

This vitamin is probably formed in the intestine by bacterial action and slowly absorbable sulphonamides inhibit this action.



This is available in tablets for oral administration and ampoules (Sodium salt) for injection : DOSE, 10 to 20 mg. daily.

The Mode of Action.—It has been suggested that folic acid acts as enzyme or co-enzyme in the synthesis of thymine required for the formation of nucleic acid, thus forming an integral part of the biological cell. Experiments showed that folic acid can be replaced by thymine. It is non-toxic even in big doses and is readily absorbed from the alimentary canal.

This is found effective in macrocytic anæmia with megaloblastic bone marrow especially in **sprue syndrome** and other nutritional macrocytic anæmias.

It is believed that folic acid exists in the body in a conjugated form. The antianæmic factor present in the liver liberates folic acid in free and active form. Megaloblastic anæmia is due to the want of liberated folic acid. In the treatment of **Addisonian pernicious anæmia** and other refractory anæmias (where the liver fraction is wanting) folic acid is not as effective and in fact may aggravate the neurological symptoms unless given with liver extract. In other cases of **macrocytic anæmia** as nutritional anæmia and in pregnancy anæmia, in pellagra and idiopathic steatorrhœa, it is quite effective and liver extract is not necessary. Folic acid is sometimes given in **granulocytopenia** and **thrombocytopenia** with pyridoxine hydrochloride.

Folic acid Antagonists.—Recently Aminopterin, A-Methopterin and Amino-an-Fol have come under investigation. These were used in acute leukæmia, neuroblastoma, carcinoma and lymphosarcoma. Aminopterin is more effective and more toxic also : dose is 1 mg. daily orally or intramuscularly for up to 5 weeks and the maintenance dose is 0.5 mg. Toxic effects are bone marrow depression, agranulocytosis and ulceration in the mouth and throat. Therefore Aminopterin is not yet safe for general use.

11 VITAMIN B₁₂.—This is another member of vitamin B complex recently isolated from the *liver substance* (Rickes and Lester Smith, 1948). It is in red crystals, many thousand times more effective in pernicious anæmia than a purified liver extract. These crystals have about 4% cobalt which has no antianæmic property and the significance of its presence is unknown.

It is believed that "Castle's extrinsic factor" is the real antianæmic principle of both liver extract and vitamin B₁₂ and the "intrinsic factor" only facilitates its absorption (Berk and Castle, 1948).

One U.S.P. unit of purified liver extract has the potency of 1 μ g. of vitamin B₁₂.

Streptomyces griseus (the source of streptomycin) can also produce this vitamin (Rickes 1948). This finding is a very important advance as 4 tons of liver can yield only 1 gramme of vitamin B₁₂ and this would mean a prohibitive expense. Like other members of vitamin B complex, the *colonic bacteria* are capable of synthesising this vitamin.

Clinical effects.—Vitamin B₁₂ causes rapid **bone marrow response**, its megaloblastic reaction changing to normoblastic one with marked reticulocytosis and increase of red blood corpuscles. **General condition** including glossitis and **neurological complications** improve just the same way as by liver extract. It is likely that this vitamin is the real antianæmic principle in liver extract but without any unfavourable reactions.

Dose.—Although 10 μ g. intramuscularly may cause remission of pernicious anæmia, in most of the severer cases, a dose of 40 to 80 μ g. weekly for the first 3 months and 30 μ g. every three week, there after (Ungley, 1949) is necessary. Oral administration is much less effective.

SUMMARY.—Thus while folic acid is the drug of choice in sprue, nutritional megaloblastic anæmia and in pregnancy anæmia, vitamin B₁₂ is the same of pernicious anæmia.

Perpolitiones Oryzæ (Rice polishings) and *Ext. Perpol. Oryz.* (each ml. contains 60 microgram of aneurine : DOSE $\frac{1}{2}$ to 1 fl. oz.). *Saccharomyces siccum* (Dried yeast), *Saccharomyces Siccum cum Creta* (Dried yeast with chalk) : DOSE, 30 to 60 grain or 2 to 4 g. *Extractum Saccharomyces siccum Concentratum* (in each g., 15 microgram. of aneurine, 60 microgram. of riboflavin and 300 microgram. of nicotinic acid). **IND. PHARM. LIST.**

COMMERCIAL PREPARATIONS.—*Nicotinic Acid*, *Niacin* also *Pelonin* and *Nicovite* (25, 50 and 100 mg. tablets) : *Nicotinamide* (50 and 100 mg. tablets and ampoules 100 mg. in 1 and 2 c.c. and in rubber capped phials) *Benicot*, tablets and ampoules also ampoules *Riboflavin* and *Nicotinamide*. *Hexabetalin* or vitamin B₆, *Benadon* (1 and 25 mg. tablets and 50 mg. per c.c. in rubber capped phials). *Folic Acid* Squibb, *Folvite* (Folic acid in 5 mg. tablets and 15 mg. in 1 c.c. ampoules).

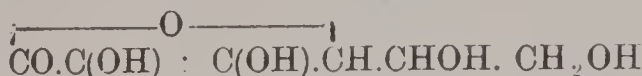
VITAMIN B COMPLEX : Orally, *Combevit* capsules : *Pulvules Becotin* and *Betalin* (with liver extract) : tablet *Beplex*, *Omni Beta*, *Becadex*, *Theravita*, *Totalin-B*, *Nutritive capsules*, *Vitaminndon B complex* : *Elixir vitamin B complex* : *Vibex liquid* : *Vitazyme*, *Plebex Elixir*, *B.G. Phosph.* and *Elixir Betalin complex* DOSE, 1 to 2 tea-spoonful t.d. *Folbesyn* contains vitamin B complex with folic acid and vitamin C, given parenterally ; *Zymafolic* capsules, multivit with folic acid, iron and liver ext.

Other B complex preparations: *Yeast tablets* (12 tablets daily) *Betamax* (wheat germ: one tea-spoonful b.d.):
By injection: *Betalin complex*, *Combex parenteral*, *Solu B* and *Hypo-beta* (in 10 c.c. Phials).

VITAMIN B₁₂ PREPARATIONS.—*Rubramin*, *Cobione*, *Vibalt.* and *Hepacobin* each containing 15 microgram in one c.c.

ACIDUM ASCORBICUM (*Acid. Ascorb.*), Vitamin C, C₆H₈O₆

ASCORBIC ACID, the enolic form of 3-keto-*l*-gulofuranlactone, may be obtained from the ripe fruits of *capsicum annuum* and other vegetable sources especially orange, lemon and tomato also potatoes or by synthesis. It contains not less than 98% of C₆H₈O₆.



Minute colourless and odourless crystals with acid taste resembling that of lemon juice, readily soluble in water and soluble in alcohol (95%), in methyl alcohol and in acetone. One gramme contains 20,000 units of antiscorbatic activity or one unit in 0.05 mg. of the standard.

DOSE, 2/5 to 1½ grain or 25 to 75 mg.: 500 to 1000 units *prophylactic* and 3 to 8 grains or 0.2 to 0.5 gramme (4000 to 10,000 units) *therapeutic*, daily.

It is easily *destroyed* by prolonged boiling especially in alkalies and neutral media and by storage. It was first isolated from the suprarenal cortex by Gyorgyl (1928).

Tabellæ Acidi Ascorbici (*Tab. Acid. Ascorb.*), See p. 56.

Pharmacology [and Therapeutics]

Ascorbic acid is essential for certain cells of **mesenchymal** origin. The intercellular material, collagen of fibrous tissue matrices of bones, dentrin and cartilage and non-epithelial binding substance as of the endothelium of the blood vessels are affected when this vitamin is deficient. As this vitamin is not stored in the tissues sufficiently, a regular intake of it is necessary almost daily.

The clinical manifestation of deficiency is **scurvy**. There are soreness and bleeding from the gums, looseness of the teeth, tenderness of the limbs with petechiæ and ecchymoses, hæmorrhage in the joints or under the periosteum: progressive loss of weight and low colour index type of **anæmia**.

An adult in health requires about 50 to 75 mg. of vitamin C daily and a growing child, twice as much in proportion to body weight: during pregnancy and lactation, 100 to 150 mg. If taken in excess, the surplus is rapidly excreted and does not cause untoward symptoms.

Vitamin C is believed to be **anti-infective** and promoting **healing of wounds** as of gastric ulcer but these have not been conclusively proved. Probably it **diminishes the toxicity** of certain drugs and heavy metals especially of arsenic.

It is probably of some value in maintaining physiological cellular activity and mineral metabolism and in hæmorrhagic diathesis. **Dermatitis** following administration of arsenical compounds may be prevented

by previous administration of ascorbic acid. Recently, it has been named *cevitamic acid*: its deficiency has been thought, although not proved, to be associated with decreased resistance to tubercular and other pulmonary infections.

[It is prescribed mainly as a preventive of scurvy (100 to 300 mg. twice or thrice daily) and also in dental caries, hypochromic anæmia, loss of appetite and in various forms of infection. Further it is required in gastro-duodenal ulcer on a deficient diet: 100 mg. 3 times daily may do. Orange, lemon and tomato juices contain this in good amount, about 0.5 mg. per c.c. and spinach has 0.9 mg. per g. These are therapeutically active. If the deficiency is great, 100 to 250 mg. of the synthetic product is required daily orally or intramuscularly].

Chemical Test for vitamin C deficiency.—Vitamin C output in the urine is proportional to its intake. So any evidence of diminished vitamin C intake is obtained by testing the urine. A blue dye, 2.6-dichlorophenol indophenol, available as tablet is reduced to a colourless form in the presence of vitamin C.

Test.—The patient passes urine and he is given orally 6 × 50 mg. tablets of vitamin C at once: the urine is collected again six hours after. This is stored in a coloured bottle. One indicator tablet dissolved in 30 c.c. of water is added to 20 c.c. of urine, acidulated if necessary. If blue colour changes to red and decolourised within half minute, the urine contains vitamin C more than 5 mg. per 100 c.c. and deficiency does not exist. If these changes do not take place, test the second sample or other samples after taking vitamin C till changes appear.

COMMERCIAL PREPARATIONS.—*Cantan* (tablet and ampoule, each 25 mg.): *Celin* and *Redoxon* (tablet 50 mg. and ampoule, 100 mg. and 500 mg.) *Cevalin* (15, 25, 50 and 100 mg. tablets and 500 mg. ampoules): *Ascorvel* (25, 50, 100 and 250 mg. tablets and 100 and 500 mg. ampoules). Vitamin C preparations are given orally, also intramuscularly and intravenously but not subcutaneously (acid in reaction).

VITAMIN P (Not official).—The water soluble, permeability vitamin, a crystalline substance of the flavone group also called *hesperidin* or *citrin* is an accessory food factor concerned in maintenance of capillary impermeability. The association of hæmorrhage and vitamin C deficiency is said to be really through this vitamin which is present in nature in ascorbic acid containing substances.

Hesperidin or *Permidin* is available in 0.25 g. oral tablets (Glaxo) 3 to 4 times daily.

Citrin in 50 mg. dose daily intravenously has been found to be of some value in capillary hæmorrhage with a tendency to form bruises. These preparations have been recently synthesised. *Rutin* was tried in capillary fragility but was not found of much substantial value (Levitt, 1948).

APPROXIMATE VITAMIN REQUIREMENTS OF A NORMAL PERSON IN INTERNATIONAL UNITS

| | Vitamin A | Vitamin B | Vitamin C | Vitamin D. |
|------------------------|------------|-----------|-----------|------------|
| Infants | 3000-7000 | 100-150 | 200-300 | 600-1000 |
| Children 2 to 8 years | 6000-8000 | 150-200 | 300-500 | 400-800 |
| Children 9 to 15 years | 8000-10000 | 300-500 | 350-600 | 400-600 |
| Adult | 3000-6000 | 300-500 | 500-800 | 300-400 |
| Pregn. and lactation | 8000-10000 | 400-600 | 900-1200 | 800-1000 |

MULTIVIT. COMMERCIAL PREPARATIONS.—*Abdec* drops, daily, 0·6 c.c. ; *Abidol C*, *Vitaminets*, *Wyamin* and *Zymacap* capsules ; *Becade*, *Esdavite*, *Multicebrin*, *Multivite* and *Multivitamindon* pills, *Zymafolic*, (multivit. with folic acid, iron and liver ext.) capsules, one or two daily.

VII. DRUGS HAVING SPECIFIC ACTION

Drugs having specific *Selective toxicity* on different infective organisms of disease (**Chemotherapy**, p. 9) may be broadly grouped as follows :

A. Those acting on the *Spirochaetes* of Syphilis (also of Yaws, Rat-bite fever, Infective jaundice and Relapsing fever) : the preparations of mercury, bismuth and arsenic : recently, penicillin also probably aureomycin.

B. Those acting on the protozoa of *Leishmaniasis* (also inguinal granuloma) : the preparations of antimony. For inguinal granuloma, chloromycetin and aureomycin.

C. Those acting on the protozoa of *Trypanosomiasis* : the preparations of arsenic, antimony and to a less extent, bismuth : also a urea compound, Suramin.

D. Those acting on the protozoa of *Malaria* : the crystalline alkaloids of cinchona, also mepacrine (atebrin) and pamaquine (plasmoquin) ; recently paludrine and others.

E. Those acting on the protozoa of *Dysentery* (amoebiasis) ; the preparations of ipecacuanha alkaloids, carbarsone, acetarsol, chiniofon, kurchi alkaloids and chloroquine, enterovioform and diodoquin also aureomycin : acting on *Flagellates* e.g. lamblia, probably mepacrine.

F. Those acting on the *Helminths* : in intestinal infection, various anthelmintics (p. 186) : for filariasis, benocide (hetrazen) and for bilharziasis, the preparations of arsenic and antimony.

G. *Bacterial infections* : the specific action in many infections has been remarkably successful, both locally and by systemic administration. The following are the examples.—(a) Acute bacterial infection : (i) *Streptococcus* : (ii) *Pneumococcus* and (iii) *Meningococcus* : sulphathiazole, sulphadiazine and sulphamerazine also penicillin, terramycin and chloromycetin. (iv) *Gonococcus* ; sulphathiazole, sulphacetamide, sulphanilamide but more effective is penicillin. (v) *B. coli* : sulphacetamide, sulphathiazole, streptomycin and aureomycin. (vi) *Staphylococcus* : sulphathiazole, sulphadiazine and penicillin (vii) *Cl. Welchii* : sulphanilamide, sulphadiazine and sulphathiazole and penicillin. (viii) *Dysentery bacilli* : sulphaguanidine and succinyl sulphathiazole. (ix) *B. pertussis*, chloromycetin and terramycin. (x) *Urinary tract* infection : penicillin, streptomycin, chloromycetin and aureomycin. (xi) *H. influenzae*, streptomycin and chloromycetin : (xii) *Rickettsial* infection,

chloromycetin and aureomycin : (xiii) *B. tuberculosis*, streptomycin and para-aminosalicylate : (xiv) *B. Lepræ* : hydnocarpus oil and sulphetrone. (xv) Certain *virus infections*, chloromycetin and aureomycin. Other chemicals of lesser possibilities are aniline and acridine dyes, quinoline, ethylhydrocupreine, phenols, hypochlorites and certain compounds of arsenic, mercury, silver and of gold.

A. Drugs having specific action on the Spirochaetes

This group includes preparations of *mercury*, *bismuth* and *arsenic* : also antibiotic, *penicillin*.

HYDRARGYRUM, (*Hydrarg.*), Mercury, *Parada.* Hg.

1. HYDRARGYRUM.

A heavy shining liquid metal, easily breakable into globules, prepared from cinnabar (native mercuric sulphide) by sublimation : contains not less than 99.5% of Hg. Insoluble in water, alcohol (95%) and in HCl.

Readily soluble in HNO_3 and boiling H_2SO_4 . On heating, readily volatilises and boils at about 358.

OFFICIAL PREPARATIONS.—(i) **Hydrargyrum cum Creta** (*Hydrarg. c. Cret.*), Powder. Mercury 33 g., dextrose 1 g. and chalk 66 g. (1 in 3). Well triturated. To be kept well-corked. Dose, 1 to 5 grains or 60 to 300 mg. (ii) **Tabellæ Hydrargyri cum Creta** (*Tab. Hydrarg. c. Cret.*), Grey powder tablets. See p. 57. Contains 85 to 116.5% of the stated amount of mercury with chalk. Dose, as of grey powder. (iii) **Pilula Hydrargyri** (*Pil. Hydrarg.*), Blue pill. See p. 52. Dose, 4 to 8 grains or 0.25 to 0.5 gramme. (iv) **Unguentum Hydrargyri** (*Ung. Hydrarg.*), Blue ointment. See p. 62. Contains 30% of Hg. (v) **Unguentum Hydrargyri Dilutum** (*Ung. Hydrarg. Dil.*), See p. 62. Mercury 10%. When mercury ointment is prescribed the dilute ointment should be supplied unless otherwise stated. (vi) **Unguentum Hydrargyri Compositum** (*Ung. Hydrarg. Co.*), *Scott's ointment*. See p. 62. Mercury 12%. (vii) **Unguentum Hydrargyri Nitratis Forte** (*Ung. Hydrarg. Nit. Fort.*), *Citrine ointment*. See p. 62. Mercury 6.7%. (viii) **Unguentum Hydrargyri Nitratis Dilutum** (*Ung. Hydrarg. Nit. Dil.*) See p. 62. Mercury 1.34%.

2. HYDRARGYRUM AMMONIATUM (*Hydrarg. Ammon.*), Ammoniated mercury, White Precipitate, (NH_2HgCl).

A white inodorous powder, prepared by the interaction of mercuric chloride and solution of ammonia. The precipitate is collected on a filter. It contains between 97 to 100.5% of NH_2HgCl . Insoluble in water and alcohol (90%) and in solvent ether : soluble in HCl.

OFFICIAL PREPARATION.—**Unguentum Hydrargyri Ammoniatum** (*Ung. Hydrarg. Ammon.*), *White precipitate ointment*. 2.5% of ammoniated mercury.

Non-official Preparations

HYDRARGYRI IODIDUM RUBRUM (*Hydrarg. Iod. Rubr.*), Red iodide of mercury, HgI_2 .—A scarlet red powder, insoluble in water, soluble in potassium iodide solution. Dose, $1/32$ to $1/16$ grain or 2 to 4 mg.

LIQUOR ARSENII ET HYDRARGYRI IODIDI.—*Donovan's solution*.

Red mercuric iodide 1, arsenic tri-iodide 1 and distilled water to 100. (Strength 1%). Dose, 5 to 15 minims or 0.3 to 1 ml.

3. **HYDRARGYRI OXIDUM FLAVUM** (*Hydrarg. Oxid. Flav.*), Yellow mercuric oxide, HgO .

An orange yellow inodorous, amorphous powder, prepared by the interaction in aqueous solution of sodium hydroxide on mercuric chloride. Contains not less than 99·3% of dry HgO . Insoluble in water and in alcohol (90%) : readily soluble in nitric acid.

OFFICIAL PREPARATIONS.—(i) **Oculentum Hydrargyri Oxidi** (*Oculent. Hydrarg. Oxid.*), See p. 51. (Strength 1%). (ii) **Oculentum Atropinæ cum Hydrargyri Oxido** (*Oculent. Atrop. c. Hydrarg. Oxid.*), See p. 51. (Strength of atropine 0·125% and yellow oxide 1%).

4. **HYDRARGYRUM OLEATUM** (*Hydrarg. Oleat.*), Mercuric oleate.

This is a semi-solid oily substance, prepared by triturating yellow mercuric oxide 200 g., liquid paraffin 50 g. and oleic acid 750 g. : used in the preparation of *Ung. Hydrarg.* Contains 20% of yellow mercuric oxide.

OFFICIAL PREPARATION.—**Unguentum Hydrargyri Oleati** (*Ung. Hydrarg. Oleat.*), 1 in 4. See p. 62.

5. **HYDRARGYRI OXYCYANIDUM** (*Hydrag. Oxycyanid.*), HgO , $3\text{Hg}(\text{CN})_2$.

This is a white crystalline powder prepared by the interaction of mercuric oxide and excess of mercuric cyanide in the presence of water : soluble 1 in 18 of water, the solution being faintly alkaline. It contains between 14·5 and 16·5% of HgO and between 83·5% and 85·5% of $\text{Hg}(\text{CN})_2$.

6. **HYDRARGYRI PERCHLORIDUM** (*Hydrag. Perchlor.*), Perchloride of Mercury, Corrosive sublimate, *Rasa Karpur*, HgCl_2 .

May be obtained by direct combination of mercury and chlorine. Contains not less than 99·5% of HgCl_2 .

Heavy, colourless or white rhombic crystalline lumps or white powder. Soluble in 18 of water and in 4 of alcohol (90%) and in ether and glycerin. When heated it fuses into a colourless liquid which next volatilises into a dense white cloud.

DOSE, $1/32$ to $1/16$ grain or 2 to 4 mg.

OFFICIAL PREPARATIONS.—**Liquor Hydrargyri Perchloridi** (*Liq. Hydrarg. Perchlor.*), See p. 49. Has $1/10$ grain in 110 minims or 0·1%. Dose, 30 to 60 minims or 2 to 4 ml.

INCOMPATIBLES.—Alkalies and their carbonates; calcium hydrate, silver nitrate, lead acetate, soaps, albumin and vegetable preparations. Potassium iodide is precipitated as red iodide of mercury which is redissolved in an excess of potassium iodide.

7. **HYDRARGYRI SUBCHLORIDUM** (*Hydrarg. Subchlor.*), Calomel, Mercurous chloride, Subchloride of mercury, HgCl .

A heavy, dull white, inodorous, nearly tasteless, powder, obtained as a sublimate, by heating together mercurous sulphate and sodium chloride. Contains not less than 99·6% of HgCl : insoluble in water, alcohol (90%), ether and in cold dilute acids.

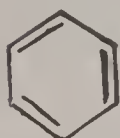
DOSE, $\frac{1}{2}$ to 3 grains or 30 to 200 mg.

OFFICIAL PREPARATIONS.—(i) **Tabellæ Hydrargyri Subchloridi** (*Tab. Hydrag. Subchlor.*), See p. 57. Strength, 89·5 to 110% of mercurous chloride (ii) **Unguentum Hydrargyri Subchloridi** (*Ung. Hydrarg. Subchlor.*), See p. 62. 20% of HgCl .

8. **MERSALYLUM** (*Mersal.*), Mersalyl, $(\text{HgOH})\text{CH}_2\text{CH}(\text{OCH}_3)\text{CH}_2\text{NHCO}\cdot\text{C}_6\text{H}_4\text{O}\cdot\text{CH}_2\text{COONa}$.

Sodium salt of salicyl (γ -hydroxymercuri- β methoxy propyl) amide-*O*-acetic acid.

Mersalyl resembling *salyrgan*, is prepared by interaction of mercuric acetate, methyl alcohol and salicylallylamide-*O*-acetic acid and conversion into sodium salt. This contains between 2.5 to 2.8% of N and 33.5 to 40.5% of Hg, the substance being dried in a vacuum desicator.



$\text{OCH}_2.\text{CO}_2\text{Na}$

$\text{CO.NH.CH}_2\text{CH}(\text{OCH}_3).\text{CH}_2.\text{HgOH}$

A white deliquescent inodorous powder with a bitter taste, soluble in 1 of water, in 3 of alcohol (95%) and insoluble in solvent ether and

in chloroform : it should be kept in a well-closed container.

Mersalyl solution containing sodium chloride or other salt becomes toxic by decomposition of mercurial complex ; this is inhibited by substances like theophylline.

OFFICIAL PREPARATION.—*Injectio Mersalyli (Inj. Mersalyl.)*, See p. 44. Strength, in 1 ml., 0.1 gm. of mersalyl, 0.05 gm. of theophylline. In 30 min. 3 gr. of mersalyl and $1\frac{1}{2}$ gr. of theophylline. Dose, 8 to 30 minims or 0.5 to 2 ml. (intramuscularly or intravenously).

9. PHENYLHYDRARGYRI NITRAS (*Phenylhydrarg. Nitras.*), $\text{C}_6\text{H}_5\text{HgOH}, \text{C}_6\text{H}_5\text{HgNO}_3$.

This, resembling *Merfenil*, is obtained by interaction of a solution of nitrogen tetroxide in ice-cold chloroform and a solution of diphenyl mercury in ice-cold chloroform and crystallisation. It should contain not less than 98% of $\text{C}_{12}\text{H}_{11}\text{O}_4\text{NHg}_2$.

White lustreless plates or crystalline inodorous powder, with a metallic and astringent taste. Sparingly soluble in cold but 1 in 160 of boiling water : moderately soluble in glycerin and fixed vegetable oils and feebly soluble in alcohol (90%).

Pharmacology [and Therapeutics]

The main actions of mercury preparations are as local *anti-septic, purgative, diuretic* and *antisiphilitic*.

Mercury, one time one of the most powerful and valuable heavy metals used in medicine, has now a limited use. It has twofold actions.

(i) **Locally**, on the tissues it has a direct approach : here, the intensity of action depends on the solubility and dissociability of Hg-ion of the different preparations. Hence the inorganic soluble compounds are more strongly poisonous and also bactericidal than the insoluble and the complex organic ones.

(ii) **Systemic action**, after absorption on the spirochaetes of syphilis and systemic toxic effects also : this is much the same in whatever form it is taken, depending on the rate of absorption and concentration in the blood.

LOCAL ACTION.—The metallic mercury and many of its salts are very diffusible and are more readily absorbed from the site of application than preparations of any other heavy metal.

Mercury is a general **protoplasmic poison** and **coagulates protein**. The albuminate compound so formed, is easily soluble in the tissue fluid containing sodium chloride and therefore a superficial protective coating is not formed to prevent penetration of mercury into the deeper tissues. Even

on the intact skin, if applied for some time, a strong solution of mercuric chloride or the undiluted salt causes deep **corrosion** and **tissue necrosis** and cause much more severe effects on the mucous membranes. This is partly due to precipitation of protein and partly to specific toxic action of mercury on all living cells. [For this caustic action, acid nitrate of mercury is sometimes used for destroying condylomata and warts].

(a) After the introduction of phenol, the next antiseptics to create even greater interest were the preparations of mercury. The intensity of action is greater with the soluble than with insoluble preparations because in the former the Hg-ion concentrates more readily on the tissues in contact. The soluble salts of mercury, as *perchloride* is very destructive to all forms of protoplasm but the insoluble ones as calomel, oxides or the organic preparations are much less active. Hence the former are largely used as **antiseptic and disinfectant**. The action is so powerful that even 1 in 100,000 solution of mercuric chloride is sufficient to kill most bacteria including anthrax if exposed to it for a few hours, and 1 in 1000 solution is considered a sufficiently powerful disinfectant²⁰²⁻²⁰⁵. It does not dissociate readily in concentrated (as 95%) alcoholic solution and is a more active antiseptic in weak solution such as 25% alcohol, (Cushny). [For the usual surgical purpose as for washing sores and douching cavities, 1 in 5000 watery solution is usually required].

Recent observations seem to show that the action is probably more **bacteriostatic** than bactericidal. The bacterial spores are often more resistant.

Probably mercury acts by being adsorbed on the surface of the bacteria, slowly penetrating inside and killing them. Hence although it acts in high dilutions, a certain time is necessary for this adsorption and penetration to occur and the presence of any other substance that can also do the same, prevents it from acting upon the bacteria. Therefore it is unsuitable for rapid disinfection and its activity is much diminished in the presence of proteins. Thus typhoid bacilli are killed in 24 hours by 1 in 1,000,000 solution of perchloride and in 2½ minutes by 1 in 1000 solution and

(202) R
Hydrarg. Perchlor. gr. 3
Pot. Iod. gr. 8·4
Eosin gr. 1/5
Aq. one pint (0·1%)
Bin-iodide lotion.

(203) R
Hydrarg. Perchlor. gr. 3
Pot. Iod. gr. 8·4
Alcohol 25% one pint
"Spirit Lotion" used for surgical purposes.

(204) R
Hydrarg. Perchlor. 0·8 g.
Acid. Hydrochlor. Dil. 60 ml.
Alcohol 95% 640 ml.
Aq. Dest. 300 ml.
Harrington's solution.
For skin disinfection.

(205) R
Hydrarg. Oxycyanid. gr. 1½
Pot. Nit. g. 70
Aq. Destill. to fl. oz. 10
Eye lotion diluted with warm water.

this is lessened by 90% by adding 3% of faecal matter. [This disability may be lessened by mixing 5 parts of sodium chloride to one of perchloride.²⁰⁶ but sodium chloride decreases ionization, astringency and cellular toxicity.] Other disadvantages are its power of causing tissue necrosis and systemic toxic effect from absorption if applied over a large surface. *Bin-iodide* and *oxycyanide* being less irritant and less corrosive are often preferred: even better is *phenyl mercuric nitrate*. The last is less toxic, more powerful (being 64 times more active on fungi and 75 times on gram-positive micro-organisms than perchloride) and only slightly inactivated by tissue fluid [and is used as antiparasitic in 1 in 1000: for wounds and fistulae 1 in 1500 and for skin disinfection 1 in 3000 solution].

(b) Mercury preparations are also destructive to many animal and vegetable parasites and are **parasiticide**²⁰⁷. Ointments of insoluble mercurials as *ammoniated mercury* and *mercury oleate* cause very little tissue destruction, but have considerable slow, antiseptic action on the skin surface. [These are frequently used in various skin affections²⁰⁸⁻²⁰⁹, and in pediculosis. These are also used as prophylactic²¹⁰ and curative for the primary sore of syphilis].

To sum up: the **disadvantages** of inorganic mercurial antiseptics are (i) slow action: (ii) inactivation in the presence of protein: (iii) tissue irritation and systemic intoxication and (iv) damage to metals especially surgical instruments. Many organic preparations have been found to be more effective with less tissue damage, less systemic intoxication and greater tissue penetrability. These include phenylmercuric nitrate, merthiolate and metaphen. Mercurochrome is bacteriostatic but feebly bactericidal.

(c) *Phenyl mercuric nitrate* is a nonirritant bacteriostatic and fungicide. It is also used as **preservative** in 0.1% solution of many injections required to be stored for some time.

It has recently been found to be an efficient **chemical contraceptive**, the killing concentration being 1/1024% in acid

-
- | | |
|--------------------------------------|----------------------------------|
| (206) R | Ol. Ricin. aa. min. 12 |
| Hydrarg. Perchlor. gr. 8.8 | Sp. Methyl. Indus. fl. oz. 1 |
| Sod. Chlorid. gr. 60 | For seborrhœa of the scalp. |
| Aq. one pint | (209) R |
| For washing sores. | Zinc. Oxid gr. 60 |
| (207) R | Ichthammol gr. 30 |
| Hydrarg. Perchlor. 4 | Ung. Hydrarg. Nit. Dil. oz. 1 |
| Acid. Acet. 75 | For chronic eczema and parasitic |
| Glycer. 75 | skin diseasea. |
| Alcohol (90%) 250 | (210) R |
| Aq. Rosæ 500 (Martindale). | Hydrarg. Subchlor. 33 |
| For destroying pediculi. | Paraff. Moll. Alb. 10 |
| (208) R | Adeps. Lan. 57 |
| Resorcin gr. 12 | Prophylactic local application |
| Hydrarg. Perchlor. gr. $\frac{1}{2}$ | against syphilis. |
| Æther. | |

and 1/256% in alkaline media (trade name, *Volpar* in collapsible tubes) and is frequently used in 0.05% water-soluble jelly].

(d) These are also **antiphlogistic** acting partly by counter-irritation²¹¹⁻²¹² and partly by diminishing the migration of the wandering cells collected at the site [and are used in various chronic inflammatory processes. The *oleate* is frequently rubbed into chronically inflamed glands or joints²¹³. Dilute *mercurial* and *compound mercurial ointments* are favourite applications for chronic inflammation of the joints and are either rubbed or applied with a tight dressing. Biniodide ointment is also helpful. A weaker mercurial ointment as that of the yellow oxide, half per cent, is applied on the lid margin in chronic inflammatory condition of the eye].

SYSTEMIC ACTION.—Mercury for therapeutic purpose, is usually given by the mouth and whatever may be the preparation, it is more or less changed in the stomach into a complex albuminate which is dissolved in sodium chloride present there. It passes down into the duodenum and if not enough to cause purgation, it is absorbed into the general circulation probably by the leucocytes and the surplus escapes with the stool as a sulphide. The soluble salts like the perchloride come in greater contact with the tissues and are more quickly absorbed.

Given by intramuscular injection, a similar albuminate is formed at the site which is probably slowly absorbed by the leucocytes. Absorption also takes place when elemental mercurial vapour is inhaled or an ointment of metallic mercury is rubbed into the skin. A part of this absorbed amount is ultimately deposited in various places especially in the liver and the kidneys: to a less extent in the spleen, intestinal wall, heart, skeletal muscles, lungs and the bones. The depot so formed may yield traces of mercury for many months after.

Excretion.—The absorbed mercury is eliminated by all the excretory organs. Thus soon after administration it is found in the *urine* and *fæces*. It is also present in the *saliva*, *sweat*, *milk* and in the foetus through placental circulation. From the liver it is excreted into the bowels with bile and is reabsorbed again so that only about 25% passes out with the *fæces* and the rest with the urine. With prolonged administration, as resulting from intramuscular injections, depots are formed at the sites of injection and also in the tissues, especially the

- (211) B
Hydrarg. Iod. Rubr. gr. 20
Adeps Benz. ad. oz. 1
Ung. For counter-irritation.
(212) B
Ung. Hydrarg. Nit. Fort.
Ung. Plumb. Subacet.
Ung. Zinc. Oxid. aa. oz. 1

- Unguentum Metallorum.*
Astringent and antiseptic.
(213) B
Hydrarg. Oleat, min. 120
Eucalyptol min. 30
Adeps Lan. Hydros. gr. 120
Paraff. Moll. Alb. ad. oz. 1
A mild counter-irritant.

kidneys and liver. During the interval of injections, this store is used up and no cumulative toxic effects are produced. But in some cases, the accumulated amount in the blood may reach toxic concentration. As long as this does not raise the renal excretion above 10 mg. daily, the kidneys are not definitely damaged but if above, toxic nephrosis results.

Mercury is given internally, either for its specific action in *syphilis*, as a *purgative* or as a *diuretic*. It was formerly used as a general *tonic* also.

(1) **Anti-syphilitic Action.**—Mercury is poisonous to all lower forms of life and especially so to the spirochaetes of *syphilis*. In the test tube, a 200,000 solution of perchloride of mercury kills them but in the blood, it must do so in much greater dilution. The action is therefore not fully direct: probably, like other chemotherapeutic agents, it acts by stimulating or aiding the manufacture of anti-syphilitic substances in the body.

A prolonged administration of mercury causes much clinical improvement and the parasites become fewer although complete sterilisation is not usually possible. This is mainly due to difficulty of maintaining the necessary therapeutic concentration in blood which is near to toxic doses. Hence on suspending the treatment, relapse is likely. Mercury does not penetrate into the cerebro-spinal fluid. So, it is of less value in neuro-syphilis as *tabes dorsalis* or the general paralysis. But in such cases, a preliminary course of mercury is safer. Organic preparations of arsenic, as arsphenamines and arsenoxides and recently penicillin are more powerful antisiphilitic drugs and are drugs of first choice, especially in the active stage of the disease. Mercury occupies a subsidiary position and given either in the intervals or alternating with them to have a sustained action. Here also bismuth is preferred being less toxic of the two. Penicillin, is so promising that it is likely to displace all chemical antisiphilitics.

METHODS OF ADMINISTRATION.—(i) *Orally*, as Grey powder in one grain dose²¹⁴⁻²¹⁶ or as perchloride of mercury solution in 30 to 60 minims doses²¹⁷⁻²¹⁸ twice or thrice daily. In the

(214) R
Hydrarg. c. Cret. gr. $\frac{1}{2}$
Glycer. Trag. q.s.
Pil. To be taken 3 times daily.
(Central Throat).

(215) R
Hydrarg. c. Cret. gr. 1
Pulv. Ipecac. et Opii gr. 2
Syr. Glucos. Liq. q.s.
(St. Bart).

Pil. Indicated if mercury causes looseness of the bowels.

(216) R
Hydrarg. c. Cret. gr. 1
Pulv. Cinnam.

Pulv. Rhei Co. aa. gr. 2
Pulv. To be taken 3 times daily.

(217) R
Liq. Hydrarg. Perchlor. min. 60
Pot. Iod. gr. 5 to 16
Glycer. min. 20
Aq. Chlorof. ad. fl. oz. 1
To be taken 3 times daily.

(218) R
Liq. Hydrarg. Perchlor.
min. 30 to 60
Sp. Chlorof. min. 15
Inf. Quass. Rec. ad. fl. oz. 1
To be taken 3 times daily.

tertiary stage of syphilis, mercury is combined with iodides. The advantage of this method is that the patient can take it himself but disadvantages are liability to gastro-intestinal disturbances, uncertain absorption and chances of discontinuing it too early. Care should be taken to avoid gastro-enteritis and the mouth should be kept very clean.

(ii) *Intramuscular injections* into the buttock : an insoluble preparation of mercury is made into an oily suspension as of metallic mercury or salicylate²¹⁹ and given once a week : one grain (60 mg.) of the metal is the usual dose. After 8 to 10 injections an interval should be given for one month. The sites of injections should be inspected for any sign of lumping and diminished absorption. The soluble preparations cause much local pain and are not used. This method of administration is now not very much advocated.

(iii) *Inunction* of the blue ointment is made on the softer skin areas as the inner side of the thighs and arms, axillæ and the abdomen, each day a different place being selected. About 60 grains are rubbed in daily for 6 days in the week for four to six weeks and then an interval is given for a month. Mercury is readily absorbed from the skin through the sweat glands and the hair follicles : also probably slightly through the lungs from the vapour inhaled during inunction and produces the systemic action. This method is getting even more out of date.

(2) **Purgative action.**—The soluble salts are too irritant to the stomach to be used as purgative. Calomel, Blue Pill and Grey Powder (the last for children), being insoluble and not so irritant, are frequently given. These pass through the stomach unchanged and in the small intestine in the alkaline juice, are changed into mercuric oxide : this in the presence of protein is slowly made into mercury albuminate and causes mild, but sustained irritation increasing the secretion of the intestinal glands. The small intestinal contents including bile are hurried down and the large intestine is also emptied quickly. But if the dose is small, there may not be much action on the colon. The bowels usually move in 8 to 10 hours. The stool is greenish from fresh bile which had no time to be altered into stercobilin. A part of the colour is also due to the formation of mercuric sulphide in the stool. As calomel is to be made into a partially soluble form, which causes irritation necessary for purgation, small repeated doses, as half grain repeated every $\frac{1}{2}$ hour upto 4 or 6 doses, act better.

(219) B

Hydrarg. Salicyl. (Neutral) gr. 1

Ol. Arachis min. 10

Intramuscularly, once a week.

[These are generally given at bed-time and must be followed by a saline purgative in the next morning, for if traces of the drug are left in the intestine, purgation continues longer than is necessary or may be partly absorbed to cause poisonous symptoms. Calomel is a favourite purgative in the beginning of nearly all acute febrile conditions.²²⁰⁻²²¹ especially malaria. It is best given in small divided doses. Blue pill²²² combined with equal parts of powdered digitalis leaves and squill (well-known Guy's Pill²²³), is frequently given in cardiac dropsy without nephritis. Grey Powder²²⁴ is a mild purgative for young children and its tastelessness is an advantage.] In minute doses, grey powder and calomel often act as **gastric sedative**²²⁵ and control vomiting.

(3) **Diuretic Action.**—After an intravenous injection of a suitable preparation as mersalyl, mercury appears in the urine in an hour but more slowly after intramuscular or oral administration. This acts as a mild irritant to the renal tubules increasing the urinary secretion.

Mercury is prescribed as a **diuretic** in cardiac and hepatic dropsy. Calomel and blue pill increase the urinary secretion, more apparent in a person with generalised oedema especially when the purgative action is not marked and a small quantity of mercury is absorbed which acts but this action is much more powerful in *mersalyl*. These, however, should not be given to a case of nephritis but are admirable in cardiac or hepatic dropsy. Simultaneous oral administration of ammonium chloride, 60 to 120 grains daily, causing mild acidosis, augments diuresis. The urinary output may be 5 pints or even more a day : but this is temporary, starting in 2 to 3 hours and nearly disappearing in 24 hours. *Toxic effects on the heart* may follow from repeated administration : these are a-v disassociation, interventricular block, broadening of Q.R.S., occasionally ventricular tachycardia even fibrillation. The new compound *Thiomerin* is not much toxic to the heart and efficient.

(220) R
Hydrarg. Subchlor.
Phenolphthal. aa. gr. 2½
Lactos. gr. 5

Pulv. Taken at bed time.

(221) R
Hydrarg. Subchlor. gr. 2
Sod. Bicarb. gr. 10

Pulv. Divide into 4 doses ; one every hour.

(222) R
Pil. Hydrarg. gr. 1½
Aloe gr. 2
Ext. Hyoscy. Sicc. gr. ½
Pil. One to be taken at bed time.

(223) R
Digit. Fol.

Scill.

Ext. Hyoscy. Sicc.

Pil. Hydrarg. aa. gr. 1

Pil. 1 to 2 pills at bed time.

(224) R
Hydrarg. c. Cret. gr. 1
Pulv. Rhei Co.
Lactos. aa. gr. 4

Pulv. 1. For a child aged one year.

(225) R
Hydrarg. Subchlor. gr. ¼
Chlorbutol gr. 2
Menthol gr. ¼
Glycer. Trag. q.s.
Pil. One every hour.

(4) **Tonic Action.**—Mercury, in minute doses continued for some time, was believed to increase the general metabolism and improve the quantity of blood and probably also increase the body weight. But in bigger doses, it has the opposite effect: this is partly due to direct action on the metabolism but probably more so from ulcerations it causes in the alimentary canal.

MAKARADHWAJA (Mercuric Sulphide), the renowned tonic of Ayurveda, probably has this kind of action, 1 to 2 grains finely pulverised, are prescribed with various excipients. The sulphate is non-irritating and in this fine impalpable form is least likely to have any local effect on the alimentary tract and a minute amount is absorbed to cause a slow and sustained tonic action.

Mercury is extensively used in Ayurveda from fairly ancient times, and the Indian physicians were the pioneers to use mercury and arsenic with considerable therapeutic skill. The preparations they commonly used were red and black sulphide (*Rasa Sindura*, *Rasa parpati*) and also perchloride (*Rasa Karpura*) internally as tonic, alterative and diuretic and also in bowel diseases, fevers and in later days, in syphilis: externally in various skin diseases.

POISONING.—The toxic effects may be *acute* as following a big dose of mercuric perchloride causing local effects of corrosion on the mucous membranes of the mouth and pharynx, also of the stomach and intestine. There is burning pain in the mouth, throat and epigastrium. Vomiting starts and shreds of mucous membrane and blood may be passed. Enterocolitis (stools containing disintegrated intestinal mucosa) and anuria follow. Signs of shock and collapse are also present. If much of the poison is thrown out with the vomit and stool, the subsequent effects may be milder and the patient gradually recovers.

Treatment.—The success depends on the dose of the poison taken and prompt treatment. Protein as milk and raw eggs are immediately given and the stomach is gently washed out. Sodium formaldehyde sulphonylate 5%, 250 c.c. may be the first lavage. For collapse isotonic saline injection with supra-renal extract is helpful.

Subacute or *chronic* poisoning results from its therapeutic administration and is more common. Mercury is badly tolerated in diseases of kidneys and the liver and in diarrhoea and dysentery. It should be given with caution in marked anæmia and cachexia. Liability to salivation is sometimes a personal idiosyncrasy [and hence, to start with, mercury should be given in small doses and if given as a purgative, a thorough clearing out by a dose of saline evacuant afterwards should be ensured. Calomel is especially liable to cause salivation]. The symptoms produced are called "**Mercurialism**".

There is metallic taste in the mouth, increase of salivary secretions, fœtor of breath and tenderness of the gums. If the drug is continued further, the glands of the mouth and throat enlarge causing extensive stomatitis with ulcerations of the soft tissues and rarely necrosis of the jaw bones.

Alimentary System.—There is often pain and heaviness in the stomach with loss of appetite, nausea and vomiting also enterocolitis, resulting in diarrhoea and progressive loss of flesh. In severe cases, the colon is ulcerated almost resembling dysenteric ulcers causing colic, tenesmus and frequent fluid motions.

Kidneys are also affected. If the irritation is mild, the renal cells are stimulated causing diuresis. But if it is severe, toxic nephritis or nephrosis results.

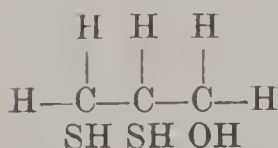
Skin eruptions are also sometimes seen especially from local application. These are either red spots of various sizes or urticarial and even eczematous patches, lasting for 1 to 3 weeks.

Nervous symptoms are sometimes seen among the industrial workers like the thermometer-makers. These are severe muscular weakness, mental changes, tremors and occasionally wrist drop. Sensory disturbances of the nature of hyperæsthesia and anæsthesia may also be present.

Treatment.—Further administration is at once stopped. A gargle containing pot. chloras 2% or tannic acid 2.5%, is often useful. Diarrhoea is controlled by dieting and administration of small doses of kaolin and opium.

In acute poisoning, sodium thiosulphate 0.3 gm. in 10 c.c. of distilled water is given intravenously every day for 8 days, dose being gradually increased. But this treatment has been nearly superseded by B.A.L.

BRITISH ANTI-LEWISITE (briefly called **BAL**) is 2:3 dimercap-topropanol or *Dimercaprol*, $\text{CH}_2\text{OH}.\text{CH}(\text{SH}).\text{CH}_2\text{SH}$, is an



example of substrate competition (p. 11 and 12). It is suggested that certain arsenic and some of the heavy metals produce their toxic action by reacting with certain essential thiol compounds present in the protoplasm, probably SH component of the pyruvate oxidase enzyme system. (Peters, 1948); these combining readily with SH group, are powerful inhibitors of the enzyme and cause toxic manifestations. Further work showed that B.A.L. can not only compete with the tissue thiol group for arsenicals but can even reverse the reaction, provided the drug is applied fairly quickly. Therapeutically B.A.L. has been found effective against poisoning by *arsenicals, mercury, bismuth, antimony, gold, chromium and nickel* but ineffective against lead, thallium and selenium. But B.A.L. itself is fairly toxic.

Doses suggested are 1.5 mg./kg. (British) and may be higher (American). It is administered intramuscularly in 5 or 10% solution in arachis oil and benzyl benzoate, first 4 hourly and from next day, twice daily. For severe poisoning, 3 mg./kg. every 4 hours on the first two days, 4 injections on the 3rd day and 2 injections for the next 10 days daily.

Available in 2 c.c. ampoules 5% oily solution, each containing 100 mg. (Boots).

If the patient is on big doses of iodides, care should be taken not to give a mercurial purgative nor even to apply mercury externally on a wide surface as highly irritating compounds may be formed by an interaction between the two at the points of elimination.

SUMMARY.—Preparations of mercury are used *externally* as antiseptic and *internally* as purgative, antisyphilitic and diuretic (especially certain organic preparations). Overdose causes mercurialism.

Non-official Preparations

MERCURIC SALICYLATE (Neutral) is given intramuscularly in syphilis $\frac{1}{2}$ to 1 gr. dose preferably with olive oil. Insoluble in water but being soluble in sodium chloride solution is readily absorbed.

MERCUROCHROME 220, Merbromin (Mercurone²²⁶, mercurihydroxy compound of sodium dibromofluorescein, green scales are readily soluble in water. It penetrates moderately, is of low toxicity but feebly antiseptic and applied in stronger solution than inorganic preparations. In 1 to 2% solution, it is used as eye-drop and also for irrigating the urethra and bladder. In alcohol-acetone solution it is used for sterilising the skin in a surgical operation.

MERTHIOLATE contains about 49% of mercury and is a powerful germicide and fungicide. For local application, 1 in 1000 and for irrigation, 1 in 5000 to 1 in 10,000 lotions are used.

NOVASUROL or **MERBAPHENE** (containing 34% of mercury).—Dose, $\frac{1}{2}$ to 2 c.c. of 10% solution, intramuscularly or intravenously. A powerful diuretic in dropsy due to conditions other than nephritis. **NOVURIT** contains in 1 c.c. 0.1 grm. of a mercury compound and 0.05 grm. of theophylline : given intravenously or intramuscularly for diuresis. **ESIDRONE** is a similar preparation.

MERCUHYDRIN, mercury with theophylline in 1 to 2 c.c. ampoule is used. Suppositories are also used : nonirritating and effective diuretic.

SALYRGAN, **NEPTAL** (36 to 40%).—Organic mercuric compound like the above, used in the same way as diuretic. Dose, $\frac{1}{2}$ to 2 c.c. of 10% solution intramuscularly or intravenously. Believed to be less toxic than the above.

THIOMERIN, disodium salt of N (gamma-carboxymethyl-mercapto-mercuri-beta-methoxy)propyl camphoramic acid, in subcutaneous dose of 2 c.c. daily or every other day is an effective diuretic and does not cause cardiac toxicity.

MERCUZANTHIN (each has 0.03 g. of mercury and 0.017 g. of anhydrous theophylline), two tablets thrice daily orally or 2 c.c. parenterally every 3rd or 4th day as diuretic is favourably reported on.

BISMUTHUM

1. BISMUTHUM PRÆCIPITATUM (*Bism. Præcip.*) :

Precipitated Bismuth.

This is obtained by the reduction of a solution of bismuth trichloride in hydrochloric acid by hypophosphorous acid : contains at least 98.5% of metallic bismuth.

A dull grey powder, easily diffusible but not soluble in water.

Dose, 1 to 3 grains or 60 to 200 mg. intramuscularly.

Injectio Bismuthi.—See p. 42, (1 in 5).

BISGLUCOL AND **BISMOSTAB** are proprietary preparations resembling this.

Dose, 8 to 15 minims or 0.5 to 1 ml. (15 minims contain 3 grains of precipitated bismuth).

(226) R

Mercurochrome 2

Aq. Dest. 35

Alcohol (95%) 55

Acetonum 10 (Martindale)

For use on skin before an operation.

2. **BISMUTHI CARBONAS** (*Bism. Carb.*); Bismuth Oxy-carbonate, Bismuth Sub-carbonate, $2(\text{Bi}_2\text{O}_2\text{CO}_3), \text{H}_2\text{O}$.

Prepared by the action of bismuth nitrate on a soluble carbonate. A white or creamy white inodorous and tasteless powder. Insoluble in water: soluble in nitric and hydrochloric acids.

Dose, 10 to 30 grains or 0.6 to 2 grammes.

Trochiscus Bismuthi Compositus (*Troch. Bism. Co.*).—Antacid lozenges. See p. 61.

3. **BISMUTHI ET SODII TARTRAS** (*Bism. et. Sod. Tart.*), Bismuth Sodium Tartrate.

Sodium Bismuthyl tartrate is obtained by the interaction of bismuth hydroxide and sodium acid tartrate. It contains between 35 and 42% of bismuth.

A white powder or slightly yellow scales, soluble at 15.5° in less than 1 part of water. It is neutral in reaction.

Dose, 1 to 3 grains or 60 to 200 mg. by intramuscular injection.

Injectio Bismuthi et Sodii Tartratis (*Inj. Bism. et Sod. Tart.*), See p. 42.

When strength is not stated, a solution containing 60 mg. per ml. or 1 gr. in 15 min. shall be dispensed.

4. **BISMUTHI OXYCHLORIDUM** (*Bism. Oxychlor.*), Bismuth Subchloride.

This is prepared by the interaction of solutions of bismuth nitrate and sodium chloride or hydrochloric acid. It contains 79 to 81% of bismuth and not less than 12.5 of chlorine.

A white, inodorous and tasteless amorphous or finely granular powder. Insoluble in water, soluble in dilute hydrochloric acid.

Dose, 10 to 30 grains or 0.6 to 2 grammes. By intramuscular injection, 1 to 3 grains or 60 to 200 mg.

Injectio Bismuthi Oxychloridi (*Inj. Bism. Oxychlor.*), See p. 42.

5. **BISMUTHI SALICYLAS** (*Bism. Salicyl.*), $\text{BiOC}_7\text{H}_5\text{O}_3$.

Obtained by the interaction of a solution of bismuth nitrate and sodium salicylate.

A white or nearly white microcrystalline tasteless, inodorous heavy powder, insoluble in water.

Dose, 10 to 30 grains or 0.6 to 2 grammes. By intramuscular injection, to 3 grains or 60 to 200 mg.

Injectio Bismuthi Salicylatis (*Inj. Bism. Salicyl.*), See p. 42.

Dose of 20 minims contains about 2 grains of bismuth salicylate to be given intramuscularly.

6. **BISMUTHI SUBGALLAS** (*Bism. Subgall.*), Bismuth oxy-gallate, basic bismuth gallate, *Dermatol.*

This is prepared by the action of gallic acid on a freshly precipitated hydrated bismuth oxide: a citron yellow, inodorous and tasteless powder, insoluble in water, dehydrated alcohol and in ether. Soluble in alkali hydroxides (making an yellow solution becoming deep red) and hot mineral acids.

Suppositoria Bismuthi Subgallatis (*Supp. Bism. Subgall.*), See p. 54.

Pharmacology [and Therapeutics]

The main actions are *local sedative, antacid and anti-syphilitic.*

Bismuth has little of the powerful local actions of other heavy metals, the chief reason being insolubility of its salts:

the main action is mechanical as *protective* especially to a wound surface. The oxychloride and the subnitrate are **mildly astringent** and **antiseptic** [and are sometimes used as dusting powder]. The wound surface is kept dry and a protective coating is formed which favours healing. Subnitrate is made into a cream also with iodoform and liquid paraffin²²⁷ and used in sinuses not healing readily. The action is probably not so much as a direct antiseptic: by keeping the wound-surface dry, it makes the place less suitable for bacterial growth: but is not altogether free from danger as a certain amount of bismuth may be absorbed and cause toxic symptoms. The subgallate is occasionally used and owing to its negative-ion, is a more powerful local **astringent** and used in piles as a suppository and on the skin as a dusting powder.²²⁸

TAKEN INTERNALLY, these form a bland coating on the mucous membranes of the stomach and the intestine which is **soothing** and **protective**. Even in big doses, bismuth preparations pass through the stomach and the intestine and as oxychloride formed in the stomach and sulphide formed in the intestine are insoluble, these are not absorbed and do not cause any symptom except when toxic impurities are present. These reduce the secretions and are mild **local astringent** [and are helpful in controlling *vomiting* and *diarrhœa*²²⁹⁻²³¹]. The **stools** are however made black by bismuth sulphide. The carbonate is an **antacid** also [and is used with other alkalies in gastric ulcer²³². It neutralises the hyperacidity and forms a protective coating on the ulcer promoting healing. But it is a weak antacid, evolves some CO₂ and taken in big doses for a long time, concretions may form. So it is not very much used]

None of these produce any of the specific effects of bismuth-ion as very little is absorbed. The subnitrate is decomposed in the intestine to form bismuth sulphide and nitrous oxide; this if in a sufficient amount, may cause nitrite

(227) R
B.I.P.P.
Bism. Subnit. 1
Iodoformum 2
Paraff. Liq. 1 or q.s.
To make a thick paste.
It is not suitable when much discharge is present.

(228) R
Hydrarg. Subchlor. gr. 30
Bism. Subgall. gr. 200
Talcum ad. oz. 2
Dusting powder.

(229) R
Bism. Carb. gr. 15
Sod. Bicarb. gr. 10
Acid. Hydrocyan. Dil. min. 4
Tinct. Cardam. Co. min. 30
Aq. Chlorof. ad. fl. oz. 1

(230) R
Bism. Subgall. gr. 20
Tannalbin gr. 7½
Ol. Cinnam. min. 1
Pulv. For diarrhœa.

(231) R
Liq. Bism. min. 30
Sod. Bicarb.
Creta aa. gr. 15
Tinct. Cardam. Co. min. 30
Aq. Menth. Pip. ad. fl. oz. 1
For acidity and diarrhœa.

(232) R
Bism. Carb.
Creta.
Mag. Carb. aa. gr. 15
Pulv. ½ hour before each feed.
For gastro-duodenal ulcer.

poisoning with cyanosis and methæmoglobinuria. In fact, the subnitrate is now-a-days seldom prescribed.

The carbonate being the least harmful is more frequently used. [In addition to gastritis and diarrhœa, it is prescribed in various kinds of colitis especially in amœbic dysentery,²³³ in 60 grains doses 3 to 4 times daily], It was formerly used as an **opaque meal** for X-raying the alimentary canal. But Barium sulphate has replaced it.

The salicylate liberates salicylic acid and is therefore a mild **antiseptic** also [and suspended in mucilage of tragacanth is prescribed for diarrhœa²³⁴].

Bismuth salts are now frequently used in **Syphilis** (Sazerac and Levediti, 1921), and also in *yaws*, *trypanosomiasis* and in *relapsing fever*. The action, as of mercury, is chemotherapeutic. This is both *spirocheticidal* and *spirochetostatic* causing both clinical and serological improvement. These cannot be given intravenously on account of toxic effects and are not absorbed from the subcutaneous tissue and are given *intramuscularly* only. The **watery solution** of pot. or sod.-bismuth tartrate, sodium bismuth citrate or bismuth thioglycollate are rapidly absorbed and excreted and effective concentration is maintained with difficulty. **Watery** or **oily suspensions** as of the official metallic bismuth, oxychloride, salicylate, hydroxide or iodo-bismuthate of quinine are more slowly absorbed and cause sustained effects. The former group requires 2 or 3 weekly intramuscular injections and the latter one only, alternating with injections of organic arsenic preparations. The usual dose is 0.1 to 0.2 gm. of bismuth. Bismuth is less active than Arsenic but is more so than Mercury especially in tertiary and congenital syphilis ; in addition, it is less toxic, prolonged treatment being possible and the injections are less painful. It has consequently replaced mercury. Thus rapid effects are obtained with arsenic which are maintained with bismuth. The modern treatment is to administer Penicillin G and this is usually sufficient in primary and early secondary stages. Later on, penicillin course may be followed by arsenic bismuth especially in resistant cases and in selected cases of cardiovascular syphilis and in neurosyphilis.

Recently (1940) an organic compound of bismuth, *Sobisminol* orally has been found as effective as one given intramuscularly : dose is 4 to 6 capsules (each capsule is 0.15 g.) daily for about 4 months. It is well tolerated and is of great promise. It may be given intramuscularly also in 10% solution twice a week ; the absorption is rapid.

(233) B
Bism. Subnit. gr. 180
Mucil. Trag. q.s.
Aq. Ment. Pip. fl. oz. 1
(Deek) 3 times daily.
Original Deek's formula is now-a-days seldom prescribed, bismuth carbonate being preferred.

(234) B
Bism. Salicyl. gr. 20
Tinct. Opii min. 5
Mucil. Trag. q.s.
Aq. Chlorof. ad. fl. oz. 1
For vomiting and diarrhœa.

ABSORPTION AND ELIMINATION.—Bismuth after absorption, accumulates in the plasma and is stored in the liver, kidneys, spleen and in the intestine. It is excreted therefrom into the mouth, stomach, small and large intestines (especially cæcum) and into the kidneys. A trace of it is found in the saliva, milk and other secretions also.

With most preparations, about nine-tenths are excreted by the kidneys. With optimum concentration of $0.5 \mu\text{g.}$ per litre in the blood, necessary for therapeutic effect, 2 to 4 mg. are excreted daily by the kidneys. (Sollmann, 1930).

Sometimes diffusion from the site of injections is slow and after several injections, like mercury, it causes cumulative toxic symptoms.

The first sign is often a slaty blue line in the gums especially of the incisor teeth. If administration is continued, stomatitis (which may be severe), vomiting and diarrhœa, jaundice and toxic nephritis follow: occasionally dermatitis. Systemic symptoms are headache, malaise, pains and aches in the limbs, muscular weakness and rarely agranulocytosis. Therefore when a patient is having injections of bismuth the condition of the liver mouth, bowels and also of the kidneys should be carefully watched.

SUMMARY.—Bismuth preparations *externally* are protective and slightly astringent: *internally*, these are **antacid** and **antidiarrhœic**. By *intramuscular injections* these are **antisymphilitic** and their toxic action is to be attended to.

Non-official Preparations

BISMUTHI SUBNITRAS.—White, inodorous, microcrystalline powder. Dose, 5 to 20 grains. (Insoluble in water, acid in reaction).

LIQUOR BISMUTHI ET AMMONII CITRAS.—Liquor Bismuthi. Dose, 30 to 60 minims. (3 grs. of bismuth in 60 minims). Used internally for gastro-intestinal disturbances.

BISMUTH OXY-IOGALLATE (*Airol*, *Airoform*²³⁵) is a non-irritating, antiseptic dusting powder.

QUININE IOGALLATE in oily suspension (in 1 c.c. 0.04 g. Bi) is given intramuscularly in syphilis.

BISMUTH TRIBROMOPHENOL (*Xeroform*²³⁶ in 5 to 20 grs. doses).

BISMUTH BETA-NAPHTHOLATE (*Orphol*, Dose, 10 to 30 grs.) and **BISMUTH SULPHO-CARBOLATE** in 2 to 8 grains doses are given as intestinal antiseptics.

BISEDIA in 60 min. contains bismuth, pepsin, morphine hydrochloride $\frac{1}{44}$ gr., dilute hydrocyanic acid, 2 min. and tincture of nux vomica min. 5. Given in dyspepsia.

BISMUTH SUBSALICYLATE (0.1 g. in oil) once a week, **SOBISMINOL** solution (0.04 g. in 2 c.c. of water) twice a week, i.m. for syphilis.

ANUSOL ointment contains bismuth subgallate 2, bismuth resorcinate 1.75, bismuth subiodide 0.037, zinc oxide 10.5, boric acid 18, balsam of Peru 2.8 and simple basis to 100. A popular pile ointment supplied in collapsible tube.

(235) R

Airoform.

Acid. Boric. aa. gr. 120

Talc. gr. 240

Dusting powder.

(236) R

Xeroform gr. 5

Pulv. Ipecac. et Opii gr. 4

Tannalbin gr. 10

Pulv. For summer diarrhœa.

ARSENICUM (*Sankha visha*)

Inorganic Arsenic Preparations

1. ARSENI TRIOXIDUM (*Arsen. Trioxid.*), Arsenious anhydride, Arsenic, Arsenious acid, As_2O_3 .

A heavy white powder or white stratified lumps, containing both transparent and opaque varieties. Prepared by roasting arsenical ores and purifying by sublimation. Contains 99.8% of As_2O_3 . Very slowly soluble at 15.5° in 65 of water.

DOSE, $1/60$ to $1/12$ grain or 1 to 5 mg.

INCOMPATIBLES.—Lime water and salts of magnesium and iron.

Liquor Arsenicalis (*Liq. Arsen.*). *Fowler's solution*.—See p. 49. (Contains $1/12$ grain of arsenic trioxide in 8 minims). Neutral in reaction.

DOSE, 2 to 8 minims or 0.12 to 0.5 ml.

Non-official Preparations

LIQUOR ARSENICI HYDROCHLORICUS.—Arsenic trioxide 1, hydrochloric acid 1.2, distilled water 100.

DOSE, 2 to 8 minims (strength 1%, acid in reaction).

LIQUOR ARSENI ET HYDRARGYRI IODIDI (*Liq. Arsen. et Hydrarg. Iod.*). *Donovan's solution*.—Arsenic tri-iodide 1, red mercuric iodide 1 and distilled water to 100. (Strength 1%, 1 grain in 110 minims).

DOSE, 5 to 15 minims or 0.3 to 1 ml.

Pharmacology [and Therapeutics]

The metalloid *Arsenic* itself is insoluble and more or less inert externally or internally but the trivalent *Arsenious acid* (H_3AsO_3) and its Oxide (As_2O_3), which is popularly known as "arsenic," are powerful poisons responsible for the characteristic arsenic action. The pentavalent arsenic acid, H_3AsO_4 , and its preparations are less poisonous and act more slowly probably by being changed to trivalent radicle. The arsenious acid-ion, however, is the really active substance concerned and is referred to as arsenic.

Further, the extent and the rapidity of dissociation of the arsenious acid ion are important. In some of the organic compounds, arsenic is combined with carbon and is of feeble toxicity. But, *in vivo*, these are slowly transformed into arsenious acid and then may cause symptoms of poisoning.

APPLIED EXTERNALLY, Arsenic has no action on the unbroken skin except on prolonged contact when it is a **rubefacient** but on a raw surface, it acts as a powerful **caustic** and was, therefore, formerly applied on cancerous growths and lupus as paste and occasionally used by dentists to destroy the pulp of a decayed tooth. But it is too poisonous to be used freely. It is **destructive** to all **living tissues**. It inhibits the growth of most bacteria in 0.01% solution and is even more poisonous to protozoa.

TAKEN INTERNALLY, in (a) *minute doses*, it increases the **appetite** and improves **digestion** and **body weight** probably by

certain specific action on the epithelia of the gastro-intestinal mucous membrane. The quantity of fat also increases and tissue oxidation is diminished. It has a selective action on the liver cells also exciting the secretion of bile; (b) but in *toxic doses* it is a powerful **irritant** and destroys these cells, causing fatty degeneration. As this destructive action follows parenteral administration also, it is presumed that this is not direct local corrosion. There is extreme dilatation of the intestinal blood vessels with much congestion and swelling of the mucous membrane causing superficial cellular destruction, extensive fatty changes in the intestine and in a number of other viscera. These cannot be explained on one hypothesis only.

A **tolerance** for it from administration in minute doses and gradually increasing, has been speculated. But this is probably due to the non-absorption or increased elimination of the drug. Prolonged administration of arsenic in soluble form, however, does not produce any tolerance, on the contrary, cumulative poisoning. (Clark).

[Arsenic is frequently prescribed as **tonic** and **alterative** in various conditions of chronic ill health as in malaria combined with iron and also in rickets and tuberculosis with calcium and vitamins and must be given after food²³⁷⁻²³⁸].

CIRCULATION.—In therapeutic doses, it has no direct action on the heart muscles. It causes slight dilatation of the capillaries and circulation of blood and lymph increases. The red bone marrow often shows changes, especially of the leucoblastic cells. There is also greater vascularity and diminution of fat cells. There may be some improvement in bone formation. But in toxic doses it acts as **capillary poison** causing wide spread vascular dilatation.

HÆMOPOIESIS.—As. does not increase the erythroblasts of the bone marrow yet it has a clinical reputation of being useful in **anæmia**²³⁹. It was formerly prescribed, in increasing doses, in primary anæmias especially in pernicious anæmia and in myeloid leukæmia. But in pernicious anæmia the liver and stomach therapy has completely replaced it. In **leukæmia** also, the results are not unequivocally promising although some improvement may follow. Fowler's solution is given orally commencing with 5 minims 3 times daily after food and gradually increased.

(237) R

Calc. Chlorid. gr. 10
Liq. Ferr. Perchlor. min. 10
Liq. Arsen. min. 3
Glycerinum min. 20
Aq. Chlorof. ad. fl. oz. 1

To be taken after food.

(238) R

Calc. Lact. gr. 10
Haliverol min. 4
Ferr. Arsen. gr. 1, 16

Lactosum gr. 10

Pulv. 2 to 3 times daily after food.

(239) R

Arsen. Triox. gr. 1/60
Ferr. Sulph. Exsicc. gr. 2
Ext. Nuc. Vom. Sicc. gr. 4
Ext. Casc. Sagr. Sicc.
Ext. Gent. aa. gr. 1

Pil. One 2 to 3 times daily after food.

Nutrition of the **skin** improves which looks fairer and the subcutaneous fat increases. Probably it acts by causing local vasodilatation and may have some specific action on the skin epithelium during excretion. But in chronic poisoning various skin eruptions appear. [It is frequently prescribed in chronic **skin diseases** especially in psoriasis, chronic eczema and pemphigus provided no acute inflammation is present].

[Arsenic is also given in increasing doses in bronchial **asthma**³⁴⁰ especially when associated with marked eosinophilia: it may be given by the mouth or better as a pentavalent organic preparation of arsenic, intramuscularly and often with benefit. It is also given in **chorea** in slowly increasing doses. The mode of action is uncertain. Arsenic is liable to cause optic neuritis and care should be taken to examine the eyes before and during its administration, if prolonged].

Arsenic is a **protozoal poison** and so it is useful in many protozoal infections but here the organic compounds are much more effective than the inorganic ones. Donovan's solution containing both arsenic and mercury was formerly prescribed in **syphilis** but is of doubtful value.

Arsenic has some reputation, next to quinine, in the treatment of chronic **malaria**³⁴¹. It, however, acts best during the convalescent stage, after quinine treatment, as a restorative and is probably of some value. It is usually prescribed along with iron³⁴².

NERVOUS SYSTEM.—Arsenic has no direct action on the central nervous system and profound depression that follows *acute poisoning* is from vascular effect. In *chronic poisoning* peripheral neuritis and in severe cases some spinal cord lesion also may appear.

EXCRETION mostly takes place in the urine and to a less extent through the alimentary canal, both stomach and intestine, the liver and the skin. Even milk contains a trace of it. This process is slow and some arsenic is retained for a long time, the bulk of which stored in the liver, to a less extent in the kidneys, the walls of the alimentary canal, spleen, cancellous bones, hairs and in the lungs.

But if given in too large a dose, or a small dose is continued too long, a group of toxic symptoms follows.

- (240) ℞
 Ammon. Carb. gr. 3
 Tinct. Lobel. Æther. min. 15
 Tinct. Bellad. min. 5
 Liq. Arsen. min. 5
 Ext. Kuth. Liq. min. 60
 Aq. Chlorof. ad. fl. oz. 1
 Three times daily after food.
- (241) ℞
 Quinin. Hydrochlor. gr. 3
 Ferr. Arsen. gr. ½
 Euonymin.

- Iridin aa. gr. ½
 Ext. Bellad. Sicc. aa. gr. ½
 Ext. Gent. q.s.
 Pil. Antimalarial.
- (242) ℞
 Ferr. et Ammon. Cit. gr. 15
 Liq. Arsenicalis min. 3
 Sp. Chlorof. min. 15
 Glycer. min. 30
 Aq. ad. fl. oz. 1
 Mix. For anæmia.

ACUTE POISONING.—Symptoms appear when arsenic in big doses is taken by the mouth with suicidal or homicidal intention : in the latter case, the poison is not detected by the victim on account of its slightly sweetish taste and white colour. Toxic symptoms may also follow intravenous injections of an arsenobenzol during the treatment of syphilis. The action believed to be due to arsenic combining with sulphhydryl compounds of the cells, thus inhibiting cellular respiration.

Given by the mouth in a big dose, in half to one hour, symptoms of severe gastro-intestinal irritation appear with a feeling of constriction in the throat, severe abdominal pain, vomiting and diarrhoea. Arsenic causes fatty degeneration and softening of the epithelia of the stomach and the intestine and although it does not coagulate protein nor causes corrosion, the effects are very much similar. It also causes wide dilatation of the capillaries and shedding of the epithelium in patches so that exudates are poured out resulting in profuse vomiting and diarrhoea, at first watery resembling the same of cholera but may afterwards be mixed with blood. Fluid loss causes severe thirst, muscular cramps and suppression of urine.

There is also profound circulatory depression with capillary paralysis and lowering of blood pressure : plasma escapes from the blood vessels especially in the splanchnic area causing watery vomiting and diarrhoea with collapse and occasionally subcutaneous oedema. Unless a sufficient amount of the poison is thrown out during vomiting and purging and not fully absorbed, death follows.

Sometimes instead of much vomiting and purging, there may be profound circulatory collapse and death. In other cases, acute symptoms may pass on to those of chronic poisoning. The fatal dose depends on the solubility and the rate of absorption : 0.1 gm. of the oxide caused death in a case.

Treatment.—If taken orally, stomach should be immediately emptied. Iron hydroxide has some reputation as an antidote. Recently such acute conditions as encephalitis, fever, stomatitis and other toxic manifestations have been treated by *dimercaprol* (*Bal*) in 10% solution in peanut oil : 3 mg. per kg. body weight is given every 4 hours for 2 days : 4 injections on the 3rd day and twice daily for 10 days or till recovery. See p. 312.

CHRONIC POISONING.—This is more common among workers in various trades and manufactories requiring the handling of arsenic : sometimes poisoning is due to prolonged intake of arsenical preparations for therapeutic purposes and less commonly, to drinking beer contaminated with arsenic during manufacture. All these result in absorption of arsenic for a long period. This takes place from the stomach and the intestine, probably also through the respiratory tract and causes cumulative poisoning.

Symptoms are due to irritation of (i) the *mucous membranes* of the eyes, nose, throat, stomach and intestine, (ii) *peripheral nerves*, (iii) *skin* and (iv) *disturbed metabolic functions*.

Thus, there may be *conjunctivitis* of varying intensity and inflammation of the upper *respiratory tract* giving rise to sneezing and short ineffectual cough. The *appetite* is often lost and vomiting and diarrhoea with colicky pain are frequently associated, less commonly, some *hepatitis* and jaundice. The onset of *peripheral neuritis* is signalled by disturbances

of sensation. Acute pain, hypersensitiveness to touch ; formications and even deficient sensibility are present in the extremities. In severe cases, motor paralysis is also present, first in the extensor muscles of the toes; later on, peronei and occasionally the flexors of the foot and leg and the extensors of the hand and fingers are involved. Usually the symptoms disappear when the poison is eliminated but occasionally some residual paralysis is left.

The skin shows brown discolouration and various types of eruption. In some cases, the epithelium is proliferated resulting in thickening (keratosis) of the hands and feet. Herpes is sometimes associated. The nails and hairs lose their lustre and become brittle.

Metabolic functions are also affected. The tissue-oxidation is diminished and protein-breakdown increased. There is diminution of glycogen and increased production of lactic acid, also fatty changes in the liver, kidneys and skeletal and heart muscles.

SUMMARY.—Inorganic arsenic preparations had been used as tonic, blood-forming agent also in some protozoal infections but toxic symptoms may appear and are now seldom used.

Non-official Preparations

FERRI ARSENAS, amorphous greenish powder, partially soluble in water. Given as pills often with iron. Dose, 1/16 to 1/4 grain.

ARSENII IODIDUM, soluble 1 in 11 of water (slightly cloudy solution).

DOSE, 1/20 to 1/5 gr. and 2 to 5 minim doses of 1% solution, dropped in milk, is useful for anæmic scrofulous children.

LIQUOR AURI ET ARSENI BROMIDI, is of doubtful value, but is given in neurasthenia. Dose, 5 to 10 minims.

ORPIMENT, As_2S_3 , (*Harital*) and REALGAR, As_2S_2 , (*Manashila*) are used in Ayurveda. These are hard, gritty masses and cause slow arsenic action.

Organic Arsenical Preparations

An organic arsenic compound has carbon atoms combined with it and this appears to lessen the toxicity. Many such compounds have been prepared and are used in various protozoal and spirochætal infections. Although comparatively innocuous outside the body, when put in contact with these organisms, *in vivo* in a condition of infection, they become more effective, satisfying Ehrlich's postulate, high parasitotropism and low organotropism.

1. ALIPHATIC SERIES (Not official).

The CACODYLATES are the earliest of the organic arsenical compounds. Taken internally, a small quantity of these is changed into inorganic form in the system. These are much less toxic than the inorganic preparations, but are mostly excreted unchanged.

CACODYLIC ACID, SODIUM CACODYLATE and GUAIACOL CACODYLATE, Dose, 1/2 to 2 grains, given by the mouth, subcutaneously or intravenously. ARRHENAL, (Disodium Methylarsenate), Dose, 2.5 to 3 grains, is used in the same way.

2. AROMATIC SERIES or Benzene series.

This has been divided into two groups ; pentavalent and trivalent.

(a) The pentavalent group.—These are less readily fixed by the colloids of the tissue and produce the specific action probably by being slowly transformed into the trivalent form.

But these are especially liable to damage the optic nerves. Their excretion is however rapid. This group includes *Tryparsamide*, *Acetarsol* and *Carbarsone*. These and *Arsphenoxide* have one benzene ring only.

Tryparsamidum (*Tryparsamid.*), $C_8H_{10}O_4N_2AsNa, \frac{1}{2}H_2O$

Tryparsamide is sodium *N*-phenylglycineamide-*p*-arsonate, prepared by boiling an aqueous solution of sodium-*p*-aminophenyl-arsonate with chloracetamide and converting the result into its sodium salt and crystallising from dilute alcohol.

$$\left\{ \begin{array}{c} OH \\ O=As- \\ ONa \end{array} \right. \text{C}_6\text{H}_5 \text{NH.CH}_2\text{CO.NH}_2 \left. \right\} \frac{1}{2}H_2O$$

A colourless, inodorous, crystalline powder, freely soluble in water, insoluble in alcohol (95%), ether, chloroform and benzene. It contains between 25.1 to 25.6% of As and between 9.25 to 9.5% of nitrogen.

Injectio Tryparsamidi (*Inf. Tryparsamid.*), See p. 48 Contains between 90 and 110% of the labelled amount of tryparsamide.

DOSE, 15 to 30 grains or 1 to 2 grammes of tryparsamide by subcutaneous, intramuscular or intravenous injection.

Pharmacology [and Therapeutics]

Tryparsamide has been found effective in **trypanosomiasis**, especially in *T. Gambiense* infection. Although not sufficiently effective in the primary and secondary stages of syphilitic infection, it has been found more active in **neurosyphilis**, its molecules readily penetrating into the central nervous system: general paralysis responds better and Tryparsamide may preferably be given after malaria therapy. It is also of some value in filarial infection.

The injections have to be continued fairly long. Usually 1 to 3 gm. are given weekly for 10 to 20 weeks. Two months' interval is given and it is started again.

About 70 to 80 gm. are necessary to obtain permanent cure (Branden). The administration is not followed by any serious constitutional symptoms or dermatitis.

TOXIC ACTIONS.—It is liable to cause optic neuritis and any dimness of vision with contraction of the visual field is the signal to stop its further administration. It may also cause vomiting, diarrhoea and occasionally fever: vasomotor disturbances and delirium may occur. As the excretion is rapid, recovery follows in most cases.

Non-official Preparations

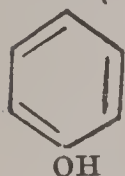
NEO-HALARSINE (Oxophenarsine Tartrate) is given in syphilis intravenously (0.045 g., 0.06 g. and 0.09 g. ampoules) once a week. Topical application in Vincent's infection is useful.

SOAMIN (Atoxyl, Arsamin), **DOSE**, $\frac{3}{4}$ to 3 grs., mostly given by intramuscular injection twice a week. Solution should be freshly made in cold sterile distilled water. It was formerly often given in filariasis, asthma, trypanosomiasis, pernicious anæmia and less commonly in syphilis. But it is gradually sinking into obscurity.

BISTROVOL (a combination of Stovarsol and soda-potash bismuth tartrate in oil), a series of 12 injections is given in 2 to 3 c.c. doses, every 3 to 6 days in syphilis and trypanosomiasis.

Acetarsol, Acetarstone, $C_8H_{10}O_5NaS$

Acetarstone also called in the trade, SPIROCID, STOVARSOL or KHAROPHEN, is 3-acetyl-amino-4-hydroxy-phenylarsonic acid, CH_3CONH , $C_6H_3(OH)AsO(OH)_2$, and prepared by the reduction of 3-nitro-4-hydroxy-phenylarsonic acid and subsequent acetylation of the amino-acid produced.



$NH.CO.CH_3$

A white crystalline powder with faintly acid taste, almost insoluble in cold and inoderately soluble in boiling water. Insoluble in alcohol (95%) and in dilute acids but soluble in dilute alkalies. It contains between 27 to 27.4% of arsenic. Dose, 1 to 4 grains or 0.06 to 0.25 gramme. (60 to 250 mg.).

Pharmacology [and Therapeutics]

This is usually available in 4 grains and $\frac{1}{2}$ gr. tablets and is prescribed orally in many protozoal infections as chronic amœbiasis, Vincent angina, lamblia infection and less commonly in syphilis, relapsing fever, yaws, chronic malaria and in some types of anæmia.

In these conditions, 2 to 3 tablets daily for 5 days are given which may be repeated with intervals of 7 days. It is not a powerful amœbicide having $\frac{1}{3}$ rd potency of earbarsone and more toxic. Acetarsol sodium or stovarsol vaginal tablets (S.V.C.) or Devegán is used in trichomonas vaginitis causing leucorrhœa : 2 tablets are introduced at bedtime followed by an alkaline douche in the next morning. These being mildly effervescent, disintegrate readily. Insufflation of the powder (12.5% of acetarsol with equal parts of light kaolin and soda bicarbonate, 4 g. is the usual single dose) with a powerful powder blower is also sometimes practised.

The excretion is slow and to be safer, in one course, one tablet 2 to 3 times daily, should be given for 8 days : an interval of two weeks should be given if a second course is to be given.

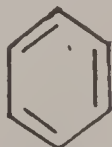
TOXIC SYMPTOMS are vomiting, diarrhœa, urticaria and generalised skin eruptions. The treatment, see p. 312.

Carbarsonum (Carbarson.), $C_7H_9O_4N_2As$

Carbarsone, *p*-carbamidophenylarsonic acid, prepared by heating *p*-aminophenylarsonic acid with urea : contains 28.1 to 28.8% As., substance being dried at 100°

A white inodorous powder with slightly acid taste, slightly soluble in water and in alcohol and soluble in alkali hydroxide and carbonate solution. Dose, 2 to 3 grains or 0.12 to 0.2 gramme.

CARBARSONE was first prepared by Ehrlich but introduced in practice by Anderson and Reed (1930). A dose of 0.25 gm. in hard gelatin capsules or tablet is given orally twice daily for 10 days : also by enema, 2 gm. dissolved in 200 c.c. of warm 1% sodium bicarbonate solution every night for 5 nights. The excretion is rather slow and if continued too long, may cause cumulative poisoning. Useful in subacute or

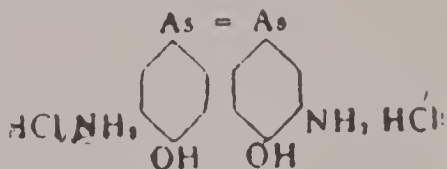


$NH.CONH_2$

chronic intestinal **amœbiasis**, being active against amœbic cysts and vegetative forms, less toxic but more effective than acetarsol. It does not cause optic injury. Gastro-intestinal symptoms may appear.

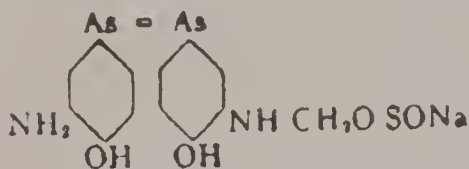
(b) **Trivalent group**.—This includes *Arsphenamine*, *Neoarsphenamine* and *Sulpharsphenamine*, also *Arsphenoxide*. The first three contain two benzene rings and all are very destructive to protozoa, especially to spirochætes of **syphilis**.

SALVARSAN (606) first prepared by Ehrlich and Hata in 1909. (Not official), is a bright yellow powder, soluble 1 in 5 of water making a syrupy liquid with acid reaction. This is arsphenamine dihydrochloride. This neutralised with 15% caustic soda solution and made to 300 c.c. with 0.5% saline solution was given intravenously. This was also now-a-days.



Neoarsphenamina, **Novarsenobenzol**, **Neosalvarsan**, 914.
 $(\text{NH}_2)(\text{OH})\text{C}_6\text{H}_3\text{As} : \text{AsC}_6\text{H}_3(\text{OH})(\text{NH} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{SONa})$.

A yellow, dry powder prepared by treating 3':3'-diamino-4:4'-dihydroxyarsenobenzene with sodium formaldehydesulphoxylate. It is soluble in water making a neutral or faintly alkaline solution. It is easily oxidised in contact with air and so is put up in sealed glass tubes exhausted of air or containing an inert gas. It contains about 20% of arsenic. It is dissolved in freshly prepared cold double distilled sterile water and must be used immediately intravenously.

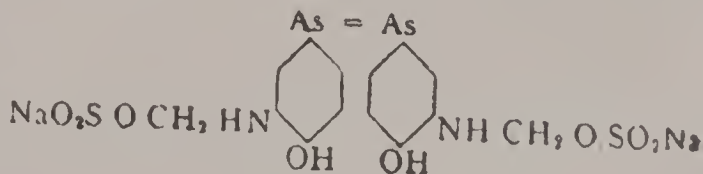


Dose, $2\frac{1}{2}$ to 10 grains or 0.15 to 0.6 gramme, by intravenous injection.

Injectio Neoarsphenaminæ (*Inj. Neoarsphenamin.*), See p. 45. The sealed container has 90 to 110% of the labelled amount of Neoarsphenamine.

Sulpharsphenamine, **Sulpharsenobenzene**, **Sulfarsenol**.
 $(\text{NH} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{SO}_2\text{Na})(\text{OH})\text{C}_6\text{H}_3\text{As} : \text{AsC}_6\text{H}_3(\text{OH})(\text{NHCH}_2 \cdot \text{O} \cdot \text{SO}_2\text{Na})$.

A yellow, dry powder, soluble in water prepared by treating 3:3'-diamino-4:4'-dihydroxyarsenobenzene dihydrochloride with formaldehyde and sodium hydrogen sulphate. Same precautions as for Neoarsphenamine are necessary in putting it up in ampoules, and sealing, storing (to be kept at 15°) and preparation of the solution for injection. The arsenical content of the compound amounts to about 32%.



Dose, $1\frac{1}{2}$ to 10 grains or 0.1 to 0.6 gramme subcutaneously or intramuscularly.

Injectio Sulpharsphenaminæ (*Inj. Sulpharsphenamin.*), See p. 47. Contains 90 to 110% of labelled amount of sulpharsphenamine.

The mother substance of all Salvarsan compounds at present available is "Old" Salvarsan or Ehrlich's Original 606, the constitutional formula of which is described. The others followed therefrom.

Pharmacology [and Therapeutics]

MODE OF ACTION.—The chemical formula of the arsphenamines is described in the form of a ring. One part of it was thought to link with the organism of the disease to which it diverted all of its poisonous actions and in that way acted as a powerful "parasitotropic" without injuring the host. (Ehrlich). But recent investigations showed, that this action is not so direct or simple. Probably these as well as bismuth preparations form compounds with tissue proteins which stimulate the defensive mechanism of the body and kill the parasites (Levaditi). Others found that after an intravenous injection, the granules of neo-arsphenamine accumulate in the reticulo-endothelial cells which probably convert these into active germicidal substances (Asua, Kuhu, Torino, 1928).

An active substance is formed there and slowly released which destroys the spirochætes. Voegtlin and Smith showed that arsphenamines with double bond linkage $R-As=As-R$ (R stands for benzene ring) were not sufficiently active till oxidised in the tissues to form $R-As=O$ (arsenoxide) and when they had this change, these were toxic either on the parasite or on the host. It is believed that arsenoxide combines with sulphadryl compound (similar to glutathione) in the protoplasm of the parasites to oxidise it to such a form that the respiratory function of the parasites stops which consequently die.

On account of their specific chemotherapeutic effects. Neo-arsphenamine and Sulpharsphenamine are frequently administered by injections for the treatment of syphilis in all its stages. The ultimate results depend very considerably on how *early* the treatment commenced and in late cases it is almost impossible to effect a complete cure. In any case, the clinical improvement is obvious after one or two injections, much more quickly than following the administration of bismuth or mercury, so that if a chancre is present, it starts healing or the skin eruptions of the secondary stage begin to fade; the spirochætes also become fewer or entirely disappear from the site. But as some of these escape destruction, injections have to be repeated fairly long with periods of interval so as to maintain a concentration of the drug in the blood for a prolonged period.

Neoarsphenamine is given *intravenously*, for quick action once a week, and although the minimum curative dose is uncertain, it is usually given in an adult, in doses increasing from 0.3 to 0.6 gm. In a weak and emaciated person, the initial dose is 0.15 gm. and the maximum dose also is comparatively less. The drug from the ampoule is dissolved in 10 c.c. of double distilled water for injection dispensed in ampoules and used immediately. Severe reactions as hyperpyrexia, vomiting, diarrhœa, vascular depression and

dysuria are indications not to increase the dose in the subsequent injection and even to reduce it. It should be given with great care if there is any inflammatory condition present in the liver, kidneys, heart, and the nervous system.

Neoarsphenamine cannot be given subcutaneously: it is an irritant and is precipitated as free base, a slow oxidation of which causes more irritation. *Sulpharsphenamine* is less readily oxidised, nonirritating and is readily absorbed from the tissue and is thus suitable for intramuscular injection, the dose being usually the same. This is more slowly absorbed and excreted. So it causes less urgent toxic symptoms and the action, although slower, is more sustained. But incidence of late toxic symptoms is not infrequent: nephritis, exfoliative dermatitis, hæmorrhagic encephalitis and bone marrow and blood dyscrasia may follow.

The effects of the arsenobenzol are usually reinforced by alternate intramuscular injections of bismuth preparations, one injection of each being given every week. Arsenoxide (*Mapharside*) is now the arsenical of choice and others are getting into the back ground. Recently Penicillin has been found to be much more effective and is given the first choice. This is followed by arsenic and bismuth preparations in resistant relapsing cases. (See Penicillin).

Syphilis of the nervous system does not respond as much probably because the arsenobenzols do not concentrate in the cerebro-spinal fluid. But incidence of neurosyphilis may be prevented by early intensive treatment.

Care should be taken in the preparation of the solution which must make a *transparent, yellow fluid*, but if cloudy or dark, it should be rejected. The solvent used must be freshly prepared with double-distilled water, previously sterilised and cooled. The solution should be used at once otherwise it may be oxidised and form toxic substances. The patient also should be prepared by giving a mild purgative on the previous night and one ounce of glucose dissolved in $\frac{1}{2}$ pint of water early next morning and the injection is to be given very slowly 3 to 4 hours after. Toxic reactions are considerably mitigated thereby.

The syringe after the injection should be mechanically cleaned as minute particles of salvarsan may stick to it, get oxidised and produce toxic reactions in a subsequent injection.

TOXIC SYMPTOMS.—Alarming symptoms are sometimes seen following an *intravenous* injection. These are fainting attacks, profuse sweating, swelling of the lips and tongue, pain in the gums and teeth, giant urticaria, severe dyspnœa, marked fall in blood pressure and cyanosis. These are called *anaphylactoid* or *nitroid crisis*, probably not due to arsenic itself but to some alteration of blood protein caused by it as in the protein of the parasites (p. 326.). Glutathione is important in carrying tissue respiration. By fixing up reduced glutathione, arsenoxide formed causes cell injury and even death. Persons hypersensitive to proteins as asthmatics are more likely to get it. This crisis usually last for about 20 minutes to one hour and sometimes longer. The crisis may be tided over by intramuscular injection of adrenaline chloride solution and atropine sulphate 1/100 gr. also ephedrine gr. $\frac{1}{2}$ with calcium gluconate 15 gr. orally. In some cases, the symptoms appear a few hours after. These are rigor with rise of temperature, headache, vomiting and diarrhœa, pain in the limbs and trunk and also herpes.

DELAYED SYMPTOMS.—In others again, the toxic symptoms appear several days or a month after. These are skin eruptions with much itching even exfoliative dermatitis, jaundice, occasionally leading to acute yellow atrophy, stomatitis, albuminuria, hæmorrhagic nephritis, severe cerebral symptoms (hæmorrhagic encephalitis) causing convulsions, coma and death : rarely polyneuritis and blood dyscrasias.

The best chemical antidote is B.A.L. (See p. 312).

These are also useful in other diseases caused by the allied protozoa of **rat-bite fever** (*Spirilla minus*), **relapsing fever** (*S. Carteri*), **sleeping sickness** (trypanosomes) and in **broncho-spirochaetosis**. In all these one course of injection is usually sufficient.

EXCRETION.—After an intravenous injection, Neoarsphenamine gets out of the blood in 3 to 4 hours and is taken up by the tissues where it is fixed in combination with nueleins. It is slowly excreted in the urine, a quantity passes out with the fæces also, this coming from the liver through bile. About 50% is eliminated in a week. It is also slightly eliminated in the perspiration, saliva and milk. The individual variations of the tissues to retain and also to excrete, are important factors governing its therapeutic efficiency. It is stored in the liver, kidneys, bone-marrow and also to a less extent in the spleen, thyroid, adrenals, heart, reproductive organs and in the brain which show traces of arsenic for about ten days after. It is probably retained longest in the cancellous tissues of the bones. The pentavalent compounds, as tryparsamide are excreted much more rapidly (p. 323).

ARSPHENOXIDE, OXOPHENARSINE (Not official)

MAPHARSIDE, MAPHARSEN (Arsenoxide) is hemialcoholate of 3-amino-4-hydroxyphenyl-arsenious oxide hydrochloride and is a single bond preparation.

This is favourably reported in the treatment of syphilis by intravenous injection weekly in doses starting from 0.02 gm. increasing to 0.06 gm., about 10 injections making a course. Several such courses are necessary. Intervals between 1st and 2nd, 2nd and 3rd and 3rd and 4th are 6, 8 and 12 weeks. During the interval, this is alternated with bismuth in 4 courses 10, 12, 16 and 16 injections.

It is probably the oxidation product through which arsphenamines are spirochetocides and consequently is more active in smaller dose. Further, nitroid crisis is unknown and gastrointestinal symptoms are rare. Being a pure chemical substance, it is more easily standardised, makes crystalloid solution with water and is more stable. It is more readily excreted than arsphenamines. Its popularity is increasing and is often given along with or after penicillin.

STANDARDISATION.—These drugs are standardised by biological test of toxicity and therapeutic activity (See page 25),

AS = O



NH₂

OH

Chemotherapy of Leishmaniasis

ANTIMONIUM

1. **ANTIMONII ET POTASSII TARTRAS** (*Antim. et Pot. Tart.*)
Tartar Emetic. Potassium Antimonyl tartrate, $C_4H_4O_7SbK$,
 $\frac{1}{2}H_2O$.

Colourless efflorescent inodorous transparent crystals or white granular powder, prepared by the combination of antimonious oxide with acid potassium tartrate. Soluble in 17 of water and in 3 of boiling water and 20 of glycerin but insoluble in alcohol 90%. It contains not less than 99% of $C_4H_4O_7SbK$, $\frac{1}{2}H_2O$.

Dose, $\frac{1}{32}$ to $\frac{1}{2}$ grain or 2 to 8 mg. ; $\frac{1}{2}$ to 1 grain or 30 to 60 mg. as emetic and $\frac{1}{2}$ to 2 grains or 30 or 120 mg. *intravenously*.

INCOMPATIBLES.—All vegetable preparations containing tannic and gallic acids, also acids, alkalies, soaps and lead salts.

Injectio Antimonii et Potassii Tartratis (*Inj. Antim. et Pot. Tart.*), See p. 42. It contains 94 to 105% of pot. antim. tart. If strength is not stated, a 2% solution is dispensed.

Dose, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. of Potassium antimonyl tartrate.

VINUM ANTIMONIALE (Not official).—Tartrated antimony 4, boiling distilled water 40 and sherry q.s. to 1000 (2 gr. in 1 oz.).

Dose, 10 to 20 minims or 0.6 to 1.2 mil. and for emetic action 120 to 240 minims.

2. **ANTIMONII ET SODII TARTRAS** (*Antim. et Sod. Tart.*)
Sodium Antimonyl-Tartrate, $C_4H_4O_7SbNa$.

Colourless transparent hygroscopic inodorous scales or powder with a sweetish taste, prepared by the interaction of antimonious oxide and sodium acid tartrate. It is soluble in 15 parts of water, insoluble in alcohol (90%). Contains not less than 90% of $C_4H_4O_7SbNa$ dried at 110° .

Dose, same as of potassium antimonyl tartrate.

Injectio Antimonii et Sodii Tartratis (*Inj. Antim. et Sod. Tart.*), See p. 42. Contains 88.5 to 105% of sod. antim. tart. If strength is not stated 1 gr. in 15 min. should be dispensed.

Dose, $\frac{1}{2}$ to 2 gr. or 30 to 120 mg. of Sodium antimonyl tartrate.

Pharmacology [and Therapeutics]

Like other heavy metals and unlike mercury, Antimony is not volatile and is therefore not quickly absorbed either from the skin or from the alimentary canal.

APPLIED EXTERNALLY to the skin, it is a fairly powerful irritant and causes small-pox like eruptions (papule changing to vesicle and finally to pustule) and is therefore unsuitable for use as counter-irritant. If the application is continued, the pustules come together and form small abscesses. If given subcutaneously, it causes intensely painful local inflammation which may terminate in suppuration and sloughing.

TAKEN INTERNALLY, Tartar emetic or Sodium antimonyl tartrate has an acrid taste and by its direct irritant action on the stomach, is a powerful **emetic**, about two grains or less being sufficient. In a slightly bigger dose, it acts as a purgative causing profuse watery evacuations. But as it causes nausea, also an uncomfortable feeling and general depression and even collapse, it is not used either as an emetic or as purgative.

POISONING.—Although severe poisoning is unknown from therapeutic oral administration, this may happen from accidental intake of a bigger amount or from taking acid drinks from certain cheap enamelled vessels in which antimony oxide was used during manufacture. Printers handling types containing antimony may also suffer.

In *acute poisoning*, an uncomfortable sensation in the stomach region is followed by frequent vomiting and often diarrhœa associated with languor and general depression.

In *chronic poisoning*, appetite is lost, general weakness, exhaustion, headache, giddiness, epigastric pain and profuse diarrhœa are often present.

Treatment.—Tannic acid is a good antidote and is used in stomach wash in 0·5% solution and afterwards 10 grains every hour with one ounce of water by the mouth.

In much smaller, subemetic doses, it is an **expectorant** acting reflexly on the bronchial mucous membrane by irritating the vagal endings in the stomach. It is also a mild **diaphoretic**, acting by dilating the cutaneous blood vessels. It was a very popular remedy in the 17th to the 19th century but is seldom used now. [Vinum antimoniale is still sometimes used in mixtures, in the early stage of acute bronchitis and other simple catarrhal fevers²⁴⁰. It loosens the secretion, favouring freer expectoration and also slightly reduces the temperature²⁴¹].

So little of it is absorbed from the alimentary canal that the actions of the antimony-ion are not seen except when it is **given intravenously**. With a fairly big dose, it acts as an **emetic** partly by the central action on the medulla and partly from its excretion into the stomach. Similar irritant action is also manifested on the intestine, leading to profuse diarrhœa and collapse. It is a powerful cardio-vascular **depressant**, reducing the force and frequency of the heart beat and also the blood pressure, probably by directly paralysing the muscles of the heart and blood vessels. It is a **vaso-dilator** also. **Respiratory movement** are also **weakened**, shorter inspirations being followed by longer expirations. Subsequently, these become slower and more irregular. In fatal cases, the lungs become congested and œdematous.

It also causes a certain amount of **depression** of the **motor system** of the spinal cord leading to muscular weakness. But these **toxic effects** are seldom seen with a dose required in therapeutic administration.

EXCRETION.—It is excreted with the fæces, bile, urine, sweat, bronchial secretions and even in milk. This is rather slow with inorganic preparations but more rapid with urea

(243) R

Pot. Antim. Tart. gr. 2

Liq. Ammon. Acet. fl. oz. 4

Sp. Æther. Nitros. fl. oz. 1

Tinct Aconit. min. 30

Syrupus fl. oz. 6 (Potter).

One tea-spoonful every 2 to 4 hours in acute bronchitis.

(244) R

Ammon. Bicarb.

Pot. Iod. aa. gr. 2

Tinct. Ipecac.

Vin. Antim. aa. min. 10

Syr. Tolu. min. 60

Aq. Camph. ad. fl. oz. 1

For subacute bronchitis.

stibamine. With a small dose, it is a mild **diuretic** but with bigger doses, it causes inflammation of the kidneys and reduces the urinary secretion. [It is therefore badly tolerated in the diseased conditions of the *intestine, lungs, liver* or of the *kidneys*].

Antimony salts have specific **chemotherapeutic action**. The mode of action is probably the same as of arsenic (p. 326). The preparations used are divided into two groups : (i) the *trivalent* organic compounds have 5 preparations, antimony potassium or sodium tartrate, antimony thioglycollamide, antimony sodium thioglycollate and stibophen : (ii) the *pentavalent* compounds are urea stibamine, stibosan, sodium antimony gluconate and neostam. The trivalent compounds are more toxic than the pentavalent, both to the host and to the parasites but are effective against bilharziasis and filariasis : pentavalent compounds are mainly used in **Kala-azar**.

[A freshly prepared 2% solution of either potassium or sodium antimony tartrate is given intravenously two or three times in a week ; starting from $\frac{1}{2}$ c.c., it is increased to 5 c.c. In children, a proportionately smaller dose is given. As a certain amount of tolerance is established only when it is given in such graduated doses, care should be taken to start with a small dose and watch for symptoms of intolerance or toxicity. These are high rise of temperature, irritating cough or vomiting immediately after the injection, also profuse watery evacuations, urticarial eruptions and afterwards signs of cardiovascular depression. In such cases, the dose should not be increased any further or rather reduced].

Anaphylactoid Syndrome.—In a few cases, immediately after the sixth or the seventh injection when the maximum dose is reached, the patient's face becomes puffy, the voice husky and his breathing difficult : a widespread urticarial rash also comes out. In a more severe case, the patient is collapsed, the pulse becomes feeble and nearly imperceptible at the wrist, breathing laboured with cyanosis and vomiting and diarrhoea set in, along with unconsciousness of variable duration. The symptoms usually disappear rapidly with injections of adrenaline hydrochloride, atropine and calcium.

More delayed toxic manifestations are loss of appetite, metallic taste in the mouth and throat, colic, entero-colitis, jaundice, headache and pain in the limbs and joints.

It is definitely *contraindicated* in acute inflammatory condition of the lungs, liver, colon and the kidneys. Even with a chronic inflammation, care should be taken in its administration. It should be given in cautious doses in advanced anæmia and in cases with oedema especially of the bases of the lungs as antimony increases the capillary transudation. In an otherwise suitable case, if during the treatment bronchial catarrh, hepatitis with jaundice, loss of appetite, metallic taste in the mouth, deficient urinary secretions and tendency to oedema appear, the drug should be temporarily stopped.

One of the earliest of the successful pentavalent compounds is *Urea Stibamine* (*p*-aminophenyl stibinic acid with urea) of Brahmachari. This is still maintaining its position and is given intravenously.

The advantage of a *pentavalent compound* is that it is stored in the system and slowly converted into the trivalent form. This slow transformation reduces the toxicity, produces a more sustained action and a larger dose may be tolerated. Therefore if the trivalent inorganic compound as sodium or potassium tartrate is either badly tolerated or the disease proves refractory, any of these pentavalent compounds should be given and if these are given from the beginning, as is more usual, the disease is cured much more quickly. The initial dose is 0.05 gm. of a preparation (for neostibosan 0.1 or 0.2 gm.) dissolved in cold sterile double distilled water and given **intravenously** twice a week. In a suitable case, injections may even be given daily, in 8 days 2 gm. or near about being administered. In such cases, the disease is cured in a shorter time. The total quantity of antimony preparation required to effect cure is variable. While some of the acute cases may be cured by about 1 gm. and chronic resistant cases requiring 3 to 5 gm., an average case of 3 to 6 months' duration requires about 2 gm. In dermal leishmaniasis, a long course of treatment extending over several months is required.

Neostibosan, Neostibene, Neostam and Sodium Antimony Gluconate are more diffusible and may be given intramuscularly. If the intravenous injection is contraindicated as in subacute or chronic pulmonary disease, chronic renal, hepatic or cardiac impairment or in children, intramuscular injections are of undoubted value. But the results are probably not quite as rapid as with intravenous injections.

Antimony is of some value in **granuloma venereum** but antibiotics as chloromycetin and aureomycin are better. In **oriental sore**, tartar emetic ointment (1 to 2%) locally and a pentavalent compound intravenously have been found successful.

In much bigger doses, an Antimony preparation is sometimes given in **Filariasis** and the trivalent salts have been found more effective than the pentavalent ones. But none of these are sufficiently dependable.

These are of some value in **sleeping sickness** and more so in **bilharziasis** given by intravenous injections as in Kala-azar but in bigger doses.

SUMMARY.—Antimony preparations, orally, are mild diaphoretic and expectorant, in bigger doses, emetic; parenterally, these are very effective in leishmaniasis (pentavalent compounds are better) and also in bilharziasis but less so in filariasis.

COMMERCIAL PREPARATIONS

UREA STIBAMINE (0.05 g. to 0.2 g. available in sterile ampoule), for intravenous injection. IND. PHARM. LIST. NEOSTIBOSAN (dose, 0.1 to 0.3 g.). NEOSTAM (sod. *p*-aminophenyl stibonate, dose is 0.05 g. to 0.5 g.), dissolved in sterile double distilled water. SODIUM ANTIMONY GLUCONATE available as PENTOSTAM (100 mg. antimony per c.c.) STIBATIN (20 mg. and 100 mg. antimony per c.c.) and STIBANATE (20 mg.) and STIBINOL (40 mg. and 100 mg. antimony per c.c.) in ampoules or 30 c.c. phials: dose of these, 20 to 100 mg. intravenously or intramuscularly slowly increased, daily, every other day or twice a week. ANTIMONY SODIUM THIOGLYCOL (ampoules of 0.5% sol.) and ANTIMONY THIOGLYCOLLAMIDE (ampoules of 0.4% sol.) are trivalent preparations similarly used.

PENTAMIDINE ISETHIONATE may be of use in leishmaniasis and trypanosomiasis (in 200 mg. ampoules) intramuscularly daily or on alternate days. Methyl glucamine Antimonate (5 c.c. contain 0.452 g. of antimony) is given i.m. every other day in leishmaniasis. Initial dose is 50 mg.

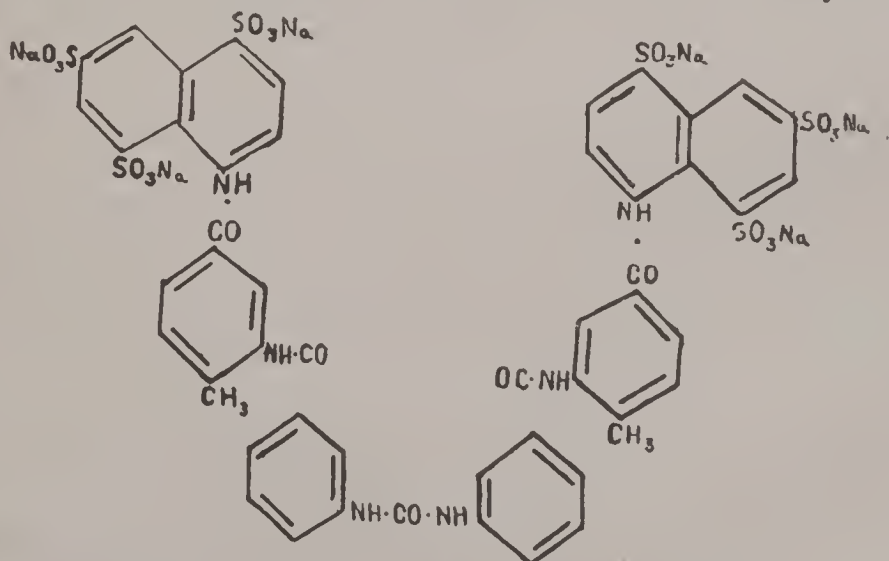
STILBAMIDINE (50 mg., 100 mg. and 150 mg. intravenously daily or every other day is used in leishmaniasis and trypanosomiasis: recently has been used in myelomatosis (at least relieves pain) and in leukæmia.

III. Chemotherapy of Trypanosomiasis and Bilharziasis

Drugs used for *trypanosomiasis* may be divided into two groups. The first includes the *arsenicals*; neoarsphenamine is of some value but much better is tryparsamide. The second is a *dye compound*, Suramin. For *bilharziasis*, antimony preparations are effective. Although potassium or sodium antimony tartrate is fairly successful, stibophen is more so.

SURAMINUM (*Suramin.*), $C_{51}H_{34}O_{23}N_6S_6Na_6$.

Suramin popularly called *Bayer 205*, Germanin, Antrypol, Fourneau 309 or Moranyl, all these being nearly identical, is chemically symmetrical urea of the sodium salt of *m* benzoyl-*m*-amino-*p*-methylbenzoyl amino-naphthalene-4 : 6 : 8 trisulphonic acid. Prepared by condensing 1-naphthylamine-4 : 6 : 8-trisulphonic acid with *m*-nitro-*p*-methylbenzoyl



chloride, reducing the product, condensing with *m*-nitrobenzoyl chloride, again reducing, treating with carbonyl chloride and neutralising with sodium hydroxide. A white or faintly cream-coloured inodorous powder

with alkaline slightly bitter taste ; freely soluble in water, only slightly in alcohol (95%) but not in solvent ether or chloroform.

Dose by intravenous injection, 15 to 30 grains or 1 to 2 grammes.

Injectio Suramini (*Inj. Suramin.*) is a sterile solution prepared by dissolving the contents of a sealed container in the required amount of water for injection immediately before use See p 47.

This is an effective chemotherapeutic drug for **trypanosomiasis** (both *gambiense* and *rhodesiense*) with curative index of about 160 and is thus a safe drug. This is administered intravenously occasionally subcutaneously, 1 gm. dissolved in 10 c.c. of distilled water and repeated on the 3rd, 10th and the 13th day and afterwards weekly about 10 gm. being usually necessary (Manson-Bahr). It is also of *prophylactic value*, a dose 2 gm. giving protection for about 3 months.

The drug is *cumulative* : sometimes causes nephritis and occasionally (dermatitis, red, itching papular rash), peripheral neuritis even amblyopia.

So the drug should be commenced with a smaller test dose and urine is examined for albumin before each injection.

Sometimes suramin is alternated with tryparsamide : in doses of 1 gm. suramin is given three times a week followed by 2 g. of tryparsamide every fifth day five injections being given.

STIBOPHENUM (*Stibophen.*), $C_{12}H_4O_{16}S_4SbNa_5, 7H_2O$.

Stibophen, popularly known as *Fouadin* or *Neo-antimosan* is sodium-antimony-bispyrocatechol-3 : 5-sodium disulphonate : obtained by the interaction of antimonious oxide, sodium pyrocatechol-3 : 5-disulphonate and sodium hydroxide. It contains between 15.6 to 16% of trivalent antimony and 16.5 to 16.9% of sulphur.

A colourless, fine, somewhat glistening, inodorous crystalline powder, readily soluble in water, almost insoluble in alcohol, solvent ether, chloroform or acetone. With water, it makes a neutral solution, at first colourless changing to lemon yellow colour.

Dose, $1\frac{1}{2}$ to 5 grains or 0.1 to 0.3 gramme by intravenous injection.

INJECTIO STIBOPHENI (*Inj. Stibophen.*).—Stibophen 6.4 g., sodium metabisulphite 0.1 g. and water for injection to 100 ml. The pH is adjusted by dilute hydrochloric acid and pot. hydrox. solution to pH 7. Distributed in ampoules, sealed and sterilised by autoclaving. See p. 47.

Dose, 25 to 75 min. or 1.5 to 5 ml. (5 ml. contains about 0.3 g. of stibophen).

This is a trivalent antimony compound and prescribed mainly in different types of **bilharziasis** in 6.4% solution intramuscularly every other day. The doses are 1.5 c.c., 3.5 c.c. and then 5 c.c. each on alternate days, about 10 to 15 injections in all are necessary containing about 4 gm. of the drug. The cure is quicker than with tartar emetic and the toxic manifestations are also less frequent.

It is also of some value in granuloma venereum, disseminated sclerosis and undulant fever. It is not used for Kala-azar.

Fantorin (6.3% solution of stibophen containing 8.6 mg. of antimony per c.c.) is a convenient preparation.

TOXIC SYMPTOMS are epigastric pain, nausea and vomiting; liver and kidney may be damaged by prolonged use.

Miracid D (also called *Nitodin*), (Not official) available in 200 mg. enteric-coated pills, in 5 to 30 mg. doses per kilo body-weight every 6 to 12 hours has been found useful in bilharziasis.

Anthiomaline (Not official) 0.5 to 4 c.c. intramuscularly twice or thrice a week has been found useful in lymphogranuloma inguinale, granuloma venereum, bilharziasis and leishmaniasis.

IV. Chemotherapy of Filariasis

Preparations of *arsenic* (tryparsamide) and of *antimony* (sod. antim. tart.) have some reputation in the treatment of filariasis. Recently *BENOCIDE* or *HETRAZAN* (diethyl carbamazine), available in 50 mg. tablets, 2 tablets given orally 3 times daily, for 2 to 3 weeks (in mild) or 3 to 4 weeks (in severe infection) has been favourably reported on: microfilaria rapidly disappears and the adults also ultimately die. This is also useful in *onchocerciasis*.

Toxic effects.—The drug itself is not much toxic: headache, lassitude, nausea and vomiting may sometimes appear: from the liberated filarial substance, allergic phenomena may be seen.

V. Chemotherapy of Malaria

The drugs used for this purpose are crystalline alkaloids of cinchona especially *quinine*: also *mepacrine*, *pamaquine* recently *paludrine* and also to some extent, certain preparations of arsenic.

Other synthetic preparations recently introduced are *Chloroquine*, *Pentaquine* and *Camaquine*.

CINCHONA (*Cinchon.*), Red Cinchona Bark

This is the dried bark of cultivated trees of *Cinchona Calisaya*, *Cinchona Ledgeriana*, *Cinchona Officinalis*, *Cinchona Succirubra* and hybrids of these species.

The bark should contain not less than 6% of the total alkaloids of which not less than half should be quinine and cinchonidine. It contains 4 crystallisable alkaloids. —*Quinine*, *Quinidine*, *Cinchonine*, *Cinchonidine* and an amorphous alkaloid *Quinoidine* (which is toxic), three acids, one glucoside, some colouring matter and a volatile oil.

CINCHONA SUCCIRUBRA (red bark), grows in large number of places as South America, Burma, Ceylon and in India (the Nilgiris and the Himalayas) and contains less quinine and more of other alkaloids.

CINCHONA CALISYA (yellow bark), grows best in Java and has a larger percentage of quinine.

Therefore for preparing "total alkaloids", the red bark and for quinine, the yellow bark are more suitable.

Powdered bark was imported into Rome from South America in 1642 (some years after the cure of Countess of Chinchon by the Jesuits). The

natives of Peru called it Kin-Kin. In 1748, Linnaeus named it *Cinchona* in honour of the Countess. The alkaloid quinine was *first isolated* by Palletier and Caventon in 1820 : it was *synthetised* by Woodward and Doering (1944)

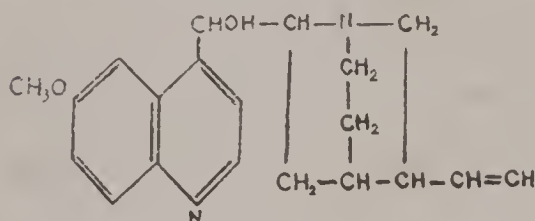
1. **TOTAQUINA** (*Totaquin.*), Total alkaloids of *Cinchona succirubra*, *C. robusta* or other varieties of *Cinchona* bark.

This contains no less than 70% of crystallisable cinchona alkaloids of which no less than 1/5th should be quinine.

A nearly colourless, yellowish grey or pale brown insoluble powder with no smell but a bitter taste. Almost insoluble in cold water, almost completely soluble in warm alcohol (95%) and in chloroform.

Dose, 5 to 10 grains or 0.5 to 0.6 gramme.

2. **QUININÆ HYDROCHLORIDUM** (*Quinin. Hydrochlor.*)
Quinine Hydrochloride, $C_{20}H_{24}O_2N_2HCl, 2H_2O$.



Silky white crystals, with a very bitter taste, soluble 1 in 32 of cold water much more freely in boiling water, and in 2 parts of alcohol (90%). The watery solution is neutral or faintly alkaline. Contains between 81 and 83% quinine. Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

Injectio Quininæ et Urethani (*Inj. Quinin. et Urethan.*).—See p. 46.
Dose, 8 to 75 minims or 0.5 to 5 mls. intravenously as a sclerosing agent.

Tabellæ Quininæ Hydrochloridi (*Tab. Quinin. Hydrochlor.*).—See p. 58.
Dose as of Quinine hydrochloride.

3. **QUININÆ DIHYDROCHLORIDUM**, (*Quinin. Dihydrochlor.*),
Quinine bi-hydrochloride, Quinine acid hydrochloride,
 $C_{20}H_{24}O_2N_2, 2HCl$.

A white or colourless microcrystalline inodorous powder with very bitter taste, obtained from quinine : freely soluble in 0.6 of water and in 12 parts of alcohol (90%) : contains 81.6% quinine.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme orally. 5 to 10 grains or 0.3 to 0.6 gramme intravenously.

Injectio Quininæ Dihydrochloridi (*Inf. Quinin. Dihydrochlor.*).—See p. 46. Dose by intravenous or intramuscular injection, 5 to 10 grains or 0.3 to 0.6 gramme. If strength is not stated, 5 gr. in 15 min. or 0.3 in 1 ml. supplied.

4. **QUININÆ SULPHAS** (*Quinin. Sulph.*), Quinine Sulphate
 $(C_{20}H_{24}O_2N_2)_2H_2SO_4, 2H_2O$.

It is in very light silky needles, inodorous, with very bitter taste. Exposed to light, tends to become brownish. Soluble in 800 of water, the solution having a bluish fluorescence. Soluble in 96 of alcohol (90%) : contains between 86 to 88% of quinine

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

One grain of it is soluble in 1 minim of dilute mineral acid in 2 fluid oz. of water. In practice 2 m. of the dilute acid is prescribed for each grain of quinine in one ounce of water.

This is in IND. PHARM. LIST as **QUININÆ SULPHAS DIHYDRATUM**.

Non-official Preparations

LIQUOR QUININÆ AMMONIATUS,—Ammoniated tincture of quinine. Quinine sulphate 20, dilute solution of ammonia 100 and alcohol (60%) to 1000. (Containing 2% w/v of quinine sulphate). Dose, 30 to 60 minims or 2 to 4 ml.

SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA.—*Easton's Syrup.*

Iron 8·6, phosphoric acid 40, strychnine hydrochloride 0·3, quinine sulphate 14·8, syrup 560, glycerin 140 and distilled water to make 1000. It contains 4/5 grain of quinin. sulph., 1/60 grain of strychnin. hydrochlor. and 1 grain of ferrous phosphate in 60 minims. Dose, 30 to 60 minims or 2 to 4 ml.

5. QUININÆ BISULPHAS (*Quinin. Bisulph.*), Quinine acid sulphate, $C_{20}H_{24}O_2N_2H_2SO_4, 7H_2O$.

Colourless transparent or opaque small needles with no smell but bitter taste : effloresces in dry air and turns yellow on exposure to light.

Soluble in 10 parts of water (making a strongly acid fluid) and in 23 parts of alcohol (90%). Containing 58 to 62% of quinine.

Dose, 5 to 10 grains or 0·3 to 0·6 gramme.

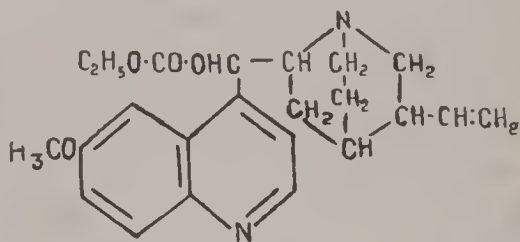
INCOMPATIBLES.—All alkaloidal precipitants specially alkalies and vegetable preparations containing tannin.

Tabellæ Quininæ Bisulphatis (*Tab. Quinin. Bisulph.*).—See p. 58. Dose, 5 to 10 grains or 0·3 to 0·6 gramme.

6. QUININÆ ET ÆTHYLIS CARBONAS (*Quinin. et Æthyl. Carb.*), Quinine ethyl carbonate, Euquinine, $C_{20}H_{23}O_2N_2.CO_2.C_2H_5$.

Prepared by the action of ethyl chlorocarbonate on quinine. Fine soft white matted needles with no smell and hardly any taste : darkens on exposure to light. Contains 80 to 82% of quinine. Slightly soluble in water : soluble in 2 parts of alcohol (90%) and freely in dilute acids. Such solutions are very bitter.

Dose, 5 to 10 grains or 0·3 to 0·6 gramme.



7. QUINIDINÆ SULPHAS (*Quinidin. Sulph.*), Quinidine Sulphate. $(C_{20}H_{24}O_2N_2)_2H_2SO_4, 2H_2O$.

This is the sulphate of an alkaloid, quinidine, obtained from cinchona bark. It contains between 82 to 87% of quinidine, $C_{20}H_{24}O_2N_2$.

Colourless needle-like crystals with a very bitter taste. Soluble at 15·5° in about 90 parts of water and 10 parts of alcohol (90%).

Dose, 1 to 5 grains or 60 to 300 mg.

Pharmacology [and Therapeutics]

The cinchona bark owes its activity to its alkaloids the most important of which is Quinine, $C_{20}H_{24}N_2O_2$.

These are quinoline derivatives. Cinchonine and Quinidine ($C_{19}H_{22}N_2O$) are isomeric. Cinchonine has a quinoline nucleus linked to quinuclidine ring through a secondary alcohol group to which is attached a vinyl group ($CH=CH_2$). Their methoxyl compounds are quinine and quinidine ($C_{20}H_{24}N_2O_2$) also isomeric. But optically, quinine and cinchonidine are lævorotatory and the other two, dextrorotatory.

APPLIED LOCALLY, quinine paralyses the sensory nerve-endings and is a local anæsthetic. The action persists for

several hours differing from other local anæsthetics as cocaine whose action is short staying. [Double salt of quinine and urea hydrochloride in 0.5 to 1% solution is sometimes given subcutaneously for local anæsthesia but a concentration of it slightly higher than necessary for anæsthesia is liable to cause tissue-necrosis].

Most of vegetable alkaloids have more or less specialised toxic action on particular parts of the body in preference to others, but quinine, although requiring much greater concentration than many of these alkaloids, is a **general protoplasmic poison** and kills all cells of the body placed in contact. At first there is slight increase of their function and this is followed by diminution of all vital processes and finally their disintegration and death. It is more active on **protozoa** than on bacteria and the action is best shown on lower organism having independent movement.

Although quinine even in 1 in 24,000 solution, lessens the phagocytic power of white cells, in therapeutic doses as 30 gr. orally daily for several days in an adult human being a concentration of 3 to 10 mg. per litre is only obtained in the blood (Clark), and such toxic effects do not follow.

Quinine has comparatively feeble action on bacteria and moulds grow freely on a solution of it.

Quinine, in 0.05% solution, **inhibits fermentation** by stopping the action of yeast and it also retards the activity of many unorganised ferments. The activity of pepsin and trypsin is increased in very diluted solution, but with a higher concentration, it is markedly reduced: that of ptyalin and diastase is also reduced, though to a less extent.

There is also diminution of **chemical activity**. Quinine restricts the normal chemical activities of tissues as synthesis, oxidation and decomposition, probably by paralysing the intracellular enzymes by whose aid these changes are brought about. These, however, do not happen with the dose of therapeutic administration.

INTERNALLY, cinchona alkaloids taken orally act locally as a **bitter** and through the gustatory nerves reflexly increase the secretions of the stomach²⁴⁵⁻²⁴⁶. [The tinctures of cinchona are often prescribed in mixtures with other bitters for chronic dyspepsia]. These have no direct action on the stomach in dilute solution though in a concentrated form and on empty stomach may paralyse the enzymes and also cause nausea and vomiting (p. 199).

(245) R
Tinct. Nuc. Vom. min. 10
Tinct. Cinchon. Co. min. 30
Sp. Ammon. Aromat. min. 20
Aq. Chlorof. ad. fl. oz. 1
One $\frac{1}{2}$ hour before food.

(246) R
Tinct. Cinchon. Co. min. 20.
Tinct. Gent. Co. min. 30
Sp. Chlorof. min. 15
Aq. Aneth. ad. fl. oz. 1
One $\frac{1}{2}$ hour before food.

Quinine is partly made into a chloride by hydrochloric acid in the stomach which passes down into the duodenum where the bulk of the absorption takes place fairly rapidly. A small fraction is precipitated by the alkaline secretion of the intestine and is passed out in the fæces unabsorbed.

EXCRETION.—It rapidly appears in the urine after administration, usually within 15 minutes, reaching the highest level in four hours : this continues for another four hours and then rapidly falls but traces may be present for the next 2 to 3 days. The main channel of excretion is urine. Only one-third, representing the unabsorbed amount, escapes with the stool and the rest is destroyed in the liver. Given intravenously, it leaves the blood plasma in a few minutes and gets attached to the corpuscles and endothelium of the capillaries either by absorption or by making firm combinations : only for a few hours a small quantity is found in the liver, kidneys, heart, lungs and in the brain (Cushny). Given intramuscularly, it takes a longer time to appear in the urine. Whatever may be the route of administration, urine is the main channel of excretion.

SPECIFIC ACTION.—Quinine has specific lethal action on the malarial parasites in the blood but the mode of action is unknown. This selective destructive action without injury to the host, is one of the dependable therapeutic achievements. The paroxysm of temperature is quickly controlled and its periodic return stopped. [In malarial fever, twenty to thirty grains of quinine (hydrochloride is better than sulphate) are given divided into 3 to 4 doses daily²⁴⁷⁻²⁵⁰. The temperature is usually controlled in two to three days. But as some parasites escape destruction, quinine has to be continued usually for seven days and afterwards periodically.

Subtertian infection requires bigger doses of quinine than benign tertian to control fever. But the tendency to *relapse* is more frequent in benign than in subtertian infection.

The exact mode of action of quinine like the same of other chemotherapeutic drugs is unknown. Many theories have been thought of. Quinine kills some parasites and liberates an antigen which causes immunity response : Quinine forms a film round the red cells and the parasites cannot enter them and die.

(247) R
Quinin. Dihydrochlor. gr. 6
Aq. q.s.
Pil. One 3 times daily.

(248) R
Quinin. Hydrochlor. gr. 5
Acid. Cit. q.s.
Pil. One 4 times daily.

(249) R
Quinin. Sulph. gr. 5
Acid. Sulph. Dil. min. 10

Glycerinum min. 30
Aq. Chlorof. ad. fl. oz. 1
One 3 times daily.

(250) R
Quinin. Sulph. gr. 5
Acid. Sulph. Dil. min. 10
Mag. Sulph. gr. 30
Sp. Chlorof. min. 30
Aq. Aneth. ad. fl. oz. 1
One 3 times daily.

Quinine acts best when the young parasites are free in the blood and have not yet entered into a fresh set of red blood corpuscles. To be most effective, it should be administered, during the apyrexial period, 3 to 4 hours before the expected paroxysm of fever so that the drug may be in maximum concentration when the young parasites are free in the circulation. But as often more than one strain of parasites are present at the same time especially in subtertian infection (several sporulations taking place daily) and the rate of absorption of the drug from the alimentary canal is also not always uniform, it is really not necessary to wait as long as that.

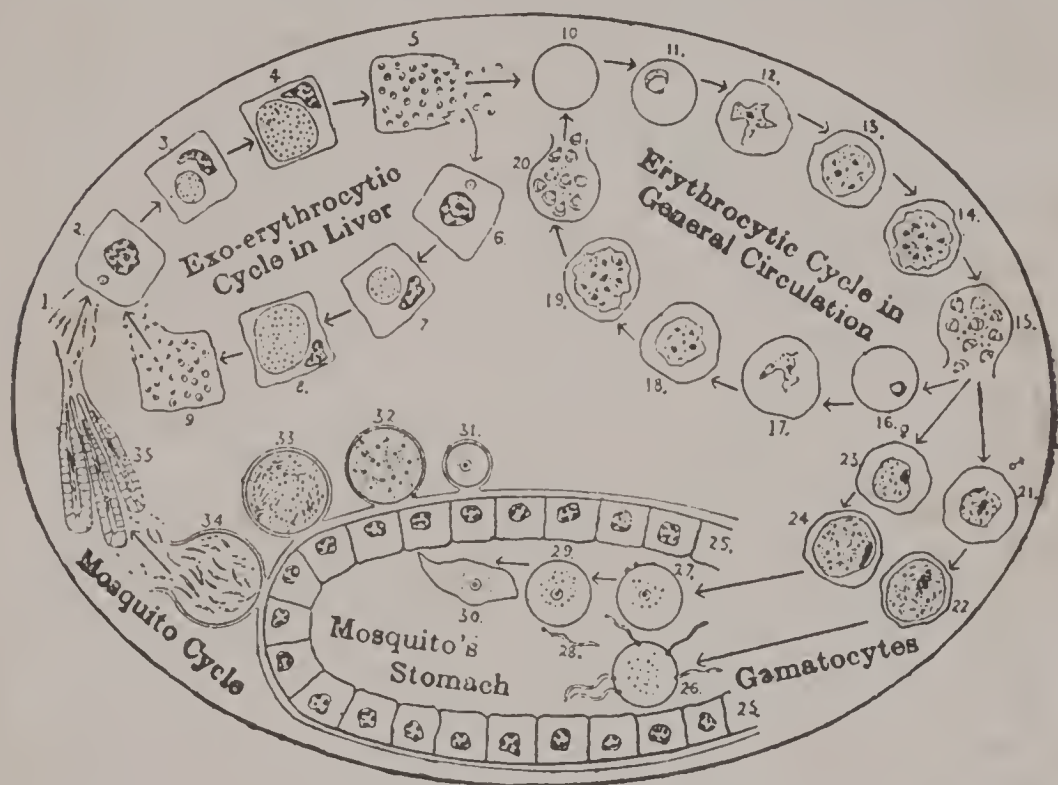
Quinine should not be given by the mouth at the height of fever because distressing vomiting if already present is now aggravated. The administration may be started as soon as sweating begins and the temperature shows a tendency to drop and in that way, the required amount of quinine gets in during the apyrexial interval. [A convenient form in most cases is *uncoated* dihydrochloride tablet or a *freshly made pill* which is swallowed without bitter taste and readily disintegrates. The absorption is helped by a preliminary purgative of calomel followed by a saline as sulphate of magnesium to bring in bile into the duodenum which is believed to help absorption and to lessen the hepatic congestion. An alkaline mixture (p. 255) should also be given an hour before each dose of quinine. As in most cases of severe attacks of malaria, a certain degree of acidosis is present and if much vomiting, ketosis is also added, a liberal supply of both alkalies and glucose is indicated.

Quinine acts best when given by the mouth in an easily disintegrable form and allowed to be absorbed by the portal stream because the malarial parasites are in largest number in the abdominal viscera. So in all cases, **oral administration should have the first choice.** But if vomited out, quinine should preferably be given intramuscularly, and in urgent cases of subtertian infection intravenously. Dihydrochloride is the drug of choice and bisulphate is decomposed when boiled. The absorption is rather slow when given intramuscularly but is still fairly dependable: the pain of injection is not too severe and muscle necrosis is almost unknown. Ten grains of quinine acid hydrochloride, in 10 c.c. of distilled water and boiled down to 3 c.c. or in 2 c.c. of autoclaved solution should be injected into the gluteal muscles preferably in successive layers and the place gently massaged to ensure diffusion. But the recent synthetic antimalarials have largely replaced this intramuscular quinine administration. Intravenous injection is often followed by a considerable fall in blood pressure and so about ten grains of quinine is given (as hydrochloride and not the acid salt) diluted with half a pint of normal saline: and adding to it $\frac{1}{2}$ to 1 c.c. of adrenaline chloride solution, is given very slowly and the whole fluid must take about half

an hour to run in. But being risky on account of chance circulatory depression, intravenous administration is to be given only after due consideration.

Although quinine rapidly cuts short a febrile paroxysm, it does not destroy all the parasites and relapses may follow.

In investigating the cause it was found that the sporozoites entering the human body from the mosquito enter into the



(After Shortt and Garnham)
 Fig. 17, 1, Sporozoites from mosquito : 2-9, cycle in liver : 10-24, cycle in general circulation : 25-34, cycle in mosquito's stomach. 35, cycle in mosquito's salivary gland

liver and habitate in the reticulo-endothelial cells, *exo-erythrocytic cycle*. There these develop by segmentation and some eventually escape into the general circulation and choose an existence and multiplication in the usual way (*erythrocytic cycle*). Quinine acts on these parasites in general circulation only but not on those in the liver and persistence of these in liver for a pretty long time, causes relapses from time to time. Search was next directed to find out a drug which could destroy both the *exo-erythrocytic* and *erythrocytic* cycles and thus cause radical cure. Several synthetic drugs have since been discovered. These are many but popular preparations are mepacrine, pamaquin, proguanil (paludrine), chloroquine and pentaquine. Their comparative value will be discussed (See p. 349). These have brought in newer avenues of improvement in antimalarial treatment and restricted the field of quinine.

Quinine may kill the **gametocytes** of benign tertian and quartan infections but not of subtertian infection (crescents) the latter being destroyed by pamaquin only.

TEMPERATURE.—In health, quinine has little action on the body temperature. But in all kinds of fever, in therapeutic doses, it is usually **slightly antipyretic**²⁴⁵ and moderately reduces the temperature. It is not quite apparent how it does so. This may be from diminished *production* or increased *loss* of heat or *depression* of the heat-regulating centre: the probabilities are more in favour of the last. There may be a slightly initial rise of temperature before its fall. But this antipyretic action is not as remarkable as in malaria.

METABOLISM.—Quinine slightly **diminishes protein metabolism** so that though the fluid portion of the urine remains unchanged, urea and other solids are some what diminished. Gaseous metabolism is not altered as the absorption of O₂ and elimination of CO₂ remain normal. Recently Hardikar proved that these do not happen with a moderate dose. [Quinine has been used in hyperthyroidism a condition with increased metabolism].

MUSCULAR TISSUES.—(i) Locally applied, quinine at first temporarily increases and then **diminishes the endurance** and the working capacity of *voluntary muscles*, these being more quickly fatigued. Given to a partially curarized muscle, it is completely curarized. The refractory period is increased and a tetanizing stimulus or acetylcholine does not cause sufficient effect. The site of this action is directly the muscle, particularly the motor end plate. [Quinine has been used in *myotonia*, a condition with tonic spasm of skeletal muscles]. Given in a concentrated solution, the **activity is lost** at once. Finally these die and pass into contracted condition.

(ii) Quinine acts on the **heart muscles** also. A small dose quickens the pulse-rate and slightly raises the blood pressure, but with a larger dose, or when given intravenously, the **heart beat is weakened** and the pulse becomes slower and feebler and the **blood pressure falls**. This fall is partly due to direct action on the heart muscles and more to dilatation of the blood vessels, quinine acting locally on the arteriolar wall and on the vaso-motor nerve-endings.

Heilig and Visveswar (I.M.G. 1944) showed that a total of 40 grains of quinine divided into 5 injections of 5, 7, 8, 10 and 10 grains given intravenously daily to malarial patients caused myocardial degeneration verified by electrocardiography.

(251) B
 Liq. Quinin. Ammon. min. 30
 Liq. Ammon. Acet. Dil. min. 60
 Tinct. Opii Camph. min. 30
 Aq. Chlorof. ad. fl. oz. 1
 A diaphoretic for catarrhal fevers.

Quinine administered intravenously destroys the intima of the vein without causing general inflammation especially if the circulation at the site is sluggish. Quinine and urethane official injection or quinine hydrochloride 0·8 grm., urethane 0·4 grm. in normal saline 2 ml. is injected into a varicose vein or piles for causing obliterating sclerosis. Properly done, this gives fairly good result painlessly without septic phlebitis.

(iii) Quinine acts on the unstripped muscles also. It increases the contractility of an isolated portion of the *uterus*, *intestine* and of the *spleen* suspended in Ringer's solution containing it. Taken orally by its action on the stomach and intestine, it may cause vomiting and diarrhoea especially with big doses and in susceptible persons. It tends to increase the contraction of pregnant uterus and should be given in cautious doses to pregnant women suffering from malaria. [It is sometimes prescribed to increase the force of uterine contraction and hasten labour.] Locally on the stomach, the sulphate is more irritant than the hydrochloride [and for therapeutic purposes, the hydrochloride preferred although the sulphate contains a slightly larger percentage of the alkaloid.]

NERVOUS SYSTEM.—In large toxic doses. it causes general depression and muscular weakness and sometimes paralysis of the medullary centres, first respiratory and then the cardiac. But with therapeutic doses, such a condition seldom happens. It is slightly analgesic but not as powerful as the coal tar products. The commoner nervous symptoms are headache, giddiness, buzzing noise in the ears and deafness, disturbances of sight, especially involving the field of vision and colour vision, and sometimes even total blindness. These effects are due to degenerative changes in the retina and the spiral ganglia in the cochlea, generally short-staying and pass off after stopping quinine, but deafness and dimness of vision may persist for many days. All these are called **cinchonism**.

BLOOD.—A single therapeutic dose generally induces some leucocytosis more involving the lymphocytes, probably from the contraction of the spleen. This is followed by leucopenia and leucocytosis again, involving more of the lymphocytes and to a less extent, the polymorphonuclear cells. Quinine causes hæmolysis in 0·5% solution only which, in therapeutic administration, is much above the fatal dose. But in susceptible people a small therapeutic dose may cause hæmolysis and precipitate malarial hæmoglobinuria (black-water fever).

The urine of patients taking quinine gives a precipitate with Mever's reagent. So this test is useful in detecting malingersers avoiding treatment.

IDIOSYNCRASY.—In addition to cinchonism, some people show hypersusceptibility to it by various skin eruptions as urticaria and erythema, or by vomiting and diarrhoea occasionally dyspnoea. Others get hæmoglobinuria even with a small dose : black-water fever is often precipitated by a dose

of quinine. These however, do not appear with the synthetic preparations and so these are more preferred.

OTHER ALKALOIDS OF CINCHONA.—Quinine and Quinidine are almost equally antimalarial and Cinchonine and Cinchonidine are less powerful. These are now a-days seldom prescribed.

TOTAQUINA.—The ideal antimalarial preparation for mass treatment in a poor country was a mixture of the total crystallisable alkaloids of cinchona bark which is much cheaper than quinine and is almost as efficacious in most cases. In all cases of benign tertian malaria, this should be used²⁵² and also sometimes in malignant tertian infection showing no pernicious symptoms. In some cases, it may cause more gastric irritation and headache than quinine. Synthetic antimalarials are also cheap and getting more popular.

CINCHONA FEBRIFUGE, a nearly colourless, pale yellowish gray or pale brown powder (IND. PHARM. LIST), contains not less than 7% of anhydrous quinine and more of the other 3 alkaloids after removal of quinine from the cinchona bark. A good sample should contain not less than 50% of crystallisable and the rest non-crystallisable alkaloids. This has got a fair amount of antimalarial property and, being much cheaper than quinine, is more suitable for mass treatment of **benign tertian malarial infection**²⁵³ in the same dose as quinine. On account of some quinoidine in it, it causes more vomiting than quinine. Its chief constituent is cinchonine which is also sometimes prescribed as **CINCHONINE HYDROCHLORIDE** or **HYDROBROMIDE** by the mouth or intramuscularly. This is fairly efficacious but is liable to cause convulsion especially in susceptible patients. Its other alkaloid, cinchonidine is believed to be more toxic and convulsant and is not prescribed separately.

QUINETUM is a mixture containing equal parts of quinine, cinchonidine and cinchonine defined by League of Nations resembling the total alkaloids of red cinchona bark. This has a more definite composition than cinchona febrifuge and hence is more preferable; prescribed in the same dose as *totaquine*.

TASTELESS QUININE.—There are two popular preparations, *Aristochin* (carbonic ester of quinine, dose 5 to 10 grains; Not official) and *Euquinine* (quinine ethyl carbonate). These are often prescribed to children who would not take bitter quinine, but owing to their insolubility, these are not readily absorbed and so are less effective. *Quinine Tannate* is also tasteless and is suitable for children but is not any better.

(252) R

Totaquin. gr. 10

Acid. Hydrochlor. Dil. min. 20

Aq. Chlorof. ad. fl. oz. 1

One 2 to 3 times daily.

(253) R

Cinchon. Febrif. gr. 10

Acid. Hydrochlor. Dil. min. 20

Aq. Chlorof. ad. fl. oz. 1

(Strain off the residue).

One 2 to 3 times daily.

The child should be given a table-spoonful of orange juice soon after ; the acid helps to dissolve these in the stomach, liberate the alkaloid and facilitate absorption.

QUINIDINE.—This is also antimalarial and some patients with quinine idiosyncrasy may tolerate it. But this is not used for malaria even in benign tertian infection.

This is more commonly used for its action on the muscles of the heart. Wenchebach (1914) first observed that cinchona alkaloids have action on heart rhythm. Frey (1918) found, quinidine is specially active.

Like quinine, quinidine depresses both voluntary and cardiac muscles. It acts more on the auricle than on the ventricle. It **prolongs the refractory period** and lessens the irritability of the auricular muscles also **reduces the rate** of auricular contraction. The sino-auricular node and auriculo-ventricular bundle are also depressed. Auriculoventricular **conduction** is somewhat lessened. All these are from direct action on the heart muscle and not through vagus. The slowing and increased diastolic period cause greater filling of the ventricles increasing the **amplitude of contraction**. [So it is used in **auricular fibrillation** also **flutter**, conditions associated with very high auricular rate. The rapid waves of "circus movements" may be broken and the normal rhythm is restored. If congestive heart failure is present, digitalis is first given which is followed up by quinidine]. It may stop **extra systole** and **paroxysmal tachycardia** by lessening the irritability of the heart muscles. But this may lower the blood pressure. Large doses may so much depress a-v bundle that the heart action may stop. The action is not uniformly reliable ; it sometimes fails or it shows personal idiosyncrasy causing nausea, vomiting, palpitation, headache and roaring noise in the ears. It is unsuitable in cases associated with much degeneration of the auricular muscles. It sometimes causes embolism from the auricles.

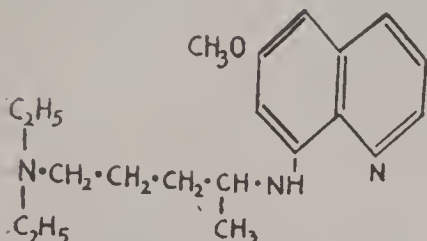
Indications.—(a) Young patient with arrhythmia of recent origin and no severe cardiac damage as in paroxysmal auricular fibrillation or flutter : (b) auricular fibrillation of Graves' disease persisting even after thyroidectomy and (c) marked palpitation with tumultuous beating of the heart.

Contra-indications.—(a) Gross myocardial damage or serious cardiac failure : (b) presence of an acute infection : (c) liability to embolism or idiosyncrasy to the drug or (d) when return to normal rhythm is unlikely as in complete heart block.

Mode of administration.—This is commenced with 3 to 5 grains orally once or twice daily increased to 6 grains every 4 hours for about 7 days or more : when the premature beats are brought under control and the normal rhythm is restored, 3 to 5 grains twice daily for a week : afterwards one dose daily for several weeks. Quinidine gluconate 5 to 7.5 grains intramuscularly causes more rapid action even in 15 minutes. Possibility of individual idiosyncrasy should be kept in mind.

SYNTHETIC ANTIMALARIALS

PAMAQUINUM, (*Pamaquin.*). $C_{42}H_{45}O_7N_3$, resembling Plasmoquine.



This may be prepared by condensation of 2-chloro-5-diethyl-aminopentane with 6-methoxy-8-aminoquinoline and treating the base with 2 : 2' dihydroxy-1 : 1'-dinaphthylmethane-3 : 3'-dicarboxylic acid. It contains between 53 to 57% of the preparation, dried at 100° for 6 hours.

The structural formula has some resemblance to that of quinine.

Yellow or orange yellow, inodorous, bitter powder, insoluble in water. Dose, $\frac{1}{4}$ to $\frac{1}{2}$ grain or 10 to 20 mg.

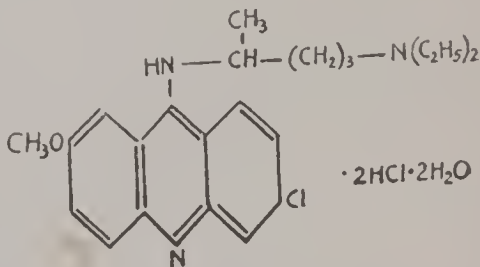
Plasmoquine (Schulemann and Roehl, 1926), is **partially effective on the trophozoites** (fever-producing cycle) of benign tertian and to some extent of quartan but not appreciably of malignant tertian malarial infection. This does not cause contraction of the pregnant uterus. But individually, its antimalarial properties are not sufficient. Its action is intensified if it is combined with quinine and is sometimes given with the latter in relapsing malaria²⁵⁴⁻²⁵⁵. Probably such a combination has *action on the exo-erythrocytic cycle*. But the much more important action is its power of **destroying gametocytes**, especially the crescents (sexual stage of subtertian malarial parasite) which no other drug can do. For this purpose, $\frac{1}{3}$ gr. 2 or 3 times daily for 3 to 5 days is sufficient. It should not be given on empty stomach and in a susceptible person it may cause cyanosis especially if continued fairly long.

TOXIC SYMPTOMS.—These are epigastric pain and occasionally cyanosis, also headache, dizziness and sweating. Cyanosis is associated with methæmoglobinæmia and methæmoglobinuria; this is more common in anæmic patients. Rarely hæmoglobinuria may also follow. The safe dose, not to exceed, is 0.04 gm. (2 tablets of $\frac{1}{2}$ gr. each) in a day.

PENTAQUINE is less toxic than pamaquin and is more suitable in combination with quinine. A daily dose not exceeding 2 g. quinine and 50 mg. pentaquine for 10 to 14 days is curative for *P. Vivax*.

MEPACRINÆ HYDROCHLORIDUM (*Mepacr. Hydrochlor.*), Quina-crine Hydrochloride, $C_{23}H_{30}ON_3Cl$, $2HCl$, $2H_2O$, resembling Atebrin, Atabrine and Metoquine.

Mepacrine hydrochloride is dihydrochloride of 2-chloro-5 (*w*-diethyl amino *a*-methylbutyl amino)-7-methoxyacridine and prepared by condensation of *w*-diethyl-amino-*a*-methylbutylamine with 2 : 5-dichloro-7-methoxyacridine and converting the base into dihydrochloride. This is an alkyl aminoacridine preparation.



$\cdot 2HCl \cdot 2H_2O$

This contains not less than 99% of $C_{23}H_{30}ON_3Cl \cdot 2HCl$, the substance dried at 130°. It is inodorous, bright yellow crystalline powder with a bitter taste. Soluble in 40 parts of water making a clear yellow solution. Dose, *prophylactic*, $1\frac{1}{2}$ gr. or 0.1 g. *Therapeutic*, 3 to 8 grains or 0.2 to 0.5 g. (in divided doses) daily.

Tabellæ Mepacrinæ Hydrochloridi (*Tab. Mepacr. Hydrochlor.*).—See p. 57. Strength is 88 to 111% of mepacrine hydrochloride. Dose as of mepacrine hydrochloride.

MEPACRINÆ METHANOSULPHONAS (*Mepacr. Methanosulph.*).
 $C_{23}H_{80}ON_3Cl$, $2CH_3SO_3H$, H_2O , resembling Atrebine Musonate.

Mepacrine methanosulphonate may be prepared by treating mepacrine in alcoholic solution with methane sulphonic acid and precipitating the methanosulphonate with ether. It contains not less than 99% of the active substance dried at 130°.

A bright yellow, inodorous, crystalline solid with bitter taste : soluble in 3 parts of water and in 36 parts of alcohol (95%).

Dose, $1\frac{1}{2}$ to 5 grains or 0.1 to 0.3 g. by intramuscular injection.

Injectio Mepacrinæ Methanosulphonatis (*Inj. Mepacr. Methanosulph.*).—See p. 44. The sealed container has between 90 and 110% of labelled amount of mepacrine methanosulphonate.

Dose, as of mepacrine methanosulphonate.

MEPACRINE, (Mietzsch and Mauss, 1930), is more effective in *controlling* the febrile **paroxysms of malaria** and it equals quinine in destroying the segmenting malarial parasites (erythrocytic cycle). It is well tolerated in quinine idiosyncrasy and in pregnancy. It is given in $1\frac{1}{2}$ gr. (0.1 grm), doses one tablet 3 times daily for 5 to 7 days. A bigger dose as 0.2 g. (2 tablets) with sod. bicarb. 15 grains is also given every 6 hours for 5 doses : then 0.1 g. 3 times daily after food for 6 days : total dose, 2.8 g. in one week. For *suppressing* the paroxysms, $1\frac{1}{2}$ gr. (0.1 g.) once daily, may be continued during whole malarial season.

It is more effective than quinine in *malignant* than in benign tertian infection although probably the action is less rapid. A blood concentration of about 0.02 mg./100 ml. is necessary.

It is more **slowly absorbed** from the alimentary canal than quinine : it is stored in the tissue causing yellow colouration of the skin and the internal organs as the liver, spleen and other viscera and may rarely cause lichenoid eruptions, even aplastic anæmia. It is **slowly excreted** in the urine taking 2 to 4 weeks after the stoppage of the administration. It is excreted in bile also but is reabsorbed from the intestine. It may occasionally precipitate an attack of hæmoglobinuria.

Although simultaneous administration of quinine and plasmoquine is helpful, atebine cannot be given with plasmoquine such combination being more toxic.

It has been found of value in **giardiasis** : 0.1 grm. in a tablet is given 3 times daily for 5 days.

Recently it has been found of value in **cardiac arrhythmia** especially auricular fibrillation acting like quinidine and has

(254) R

Plasmoquin gr. 1, 24

Aristochin gr. 2

Lactosum gr. 3

For a child 2 to 5 years old.

(255) R

Quinin. Hydrochlor. gr. 3

Plasmoquin. gr. $\frac{1}{6}$

Mucil. Trag. q.s. Pil.

One 3 times daily.

been used in hyperthyroidism and in arteriosclerotic heart disease (Gertler and Yohalem, 1949). Dose proposed is 0.3 to 0.6 g. in 10 c.c. of 1% procaine solution intramuscularly.

MEPACRINE METHANOSULPHONATE, ATEBRIN MUSONATE or *Quinacrine soluble* in 0.3 gm. dose is given intramuscularly (*not intravenously*) usually in a single and in a low patient in 2 or 3 divided doses dissolved in sterile double distilled water. This is readily absorbed, does not cause much local pain and usually 3 injections bring down the fever. It is especially suitable in subtertian infection with pernicious symptoms when oral administration is not possible.

Advantages of Mepacrine (atebrin or atabrine) over quinine are many. (a) It is more pleasant to take and does not cause cinchonism nor much vomiting: (b) does not act on the uterus and can be used in late pregnancy: (c) safer in black-water fever: (d) course of treatment is shorter, more effective in subtertian infection and relapse rate is less: (e) quick mass production of the drug is possible at a cheap rate.

TOXIC MANIFESTATIONS are comparatively few. The dye causes temporary yellow colouration of the skin which is not toxic. Given on empty stomach, it may cause abdominal pain. It sometimes causes cerebral symptoms such as mental depression, stupor, coma or delirium: rarely skin eruptions. These are treated symptomatically.

OTHER SYNTHETIC PREPARATIONS

1. PROGUANIL or PALUDRINE, N_1 -*p*-chlorophenyl- N_5 -isopropyl-biguanidine, available in 0.1 gm. colourless tablets has been found quite effective especially in subtertian malaria. It is easily absorbed from oral administration, reaching highest blood concentration in 4 hours. The blood level reached is relatively low but the drug concentrates more in lung, liver, spleen and kidneys and more so in the red and white blood corpuscles. It is metabolized to a compound active against malaria. It is a *causal prophylactic* against mosquito-introduced subtertian malaria and is a *partial prophylactic* against vivax malaria. It kills both the erythrocytic and the exo-erythrocytic parasites of subtertian malaria thus preventing the relapse also. But it only suppresses the exo-erythrocytic parasites of vivax infection: so that when the administration is stopped, the paroxysm returns. It is thus of great curative value, suppressing the paroxysm and preventing relapse of subtertian malaria but less effective in the vivax form. Elimination is mainly in the urine and less so in the stool. Toxic symptoms are negligible (may be vomiting rarely hæmaturia) and being colourless, the skin is not coloured.

Dose suggested for the paroxysm is 3 tablets at a time twice daily (0.6 g.) for 10 days. In benign tertian infection, a single dose of 0.3 g. is followed by the suppressive course: in addition one tablet twice a week for 6 months. *Suppressive treatment* in

an endemic area is 3 tablets once weekly, 2 tablets twice weekly or one tablet daily for many weeks. Gametocytes after administration of one tablet t.d. fail to develop in the mosquito (indirect gametocytic). But it tends to make patients *drug-fast* and is not thus suitable for mass treatment.

CAMAQUIN, in 0.2 g. tablets, 3 to be given as a single dose: this brings down the temperature: *suppressive dose*: this every 2 weeks, during the season.

2. CHLOROQUINE, Aralen is used as Diphosphate: it is effective against the erythrocytic form of both vivax and subtertian malaria but ineffective against the exo-erythrocytic form of vivax infection. So the radical cure results in subtertian but not in vivax infection which tends to relapse.

Dose, 1 g. or 4 tablets followed in 6 hours by 0.5 g. daily for next 3 days, total dose, 2.5 g. For suppressive treatment, 0.5 g. weekly suffice. It is also of great value in *amaebiasis* especially if *subacute hepatitis* is also present. *Dose*, 1 g. daily for 2 days followed by 0.5 g. daily for 2 to 3 weeks.

TOXIC SYMPTOMS are insomnia, gastro-intestinal irritation, pain in the abdomen and pruritus.

The effective antimalarial drugs, (a) for *erythrocytic form*, quinine, proguanil, mepacrine, chloroquine and less so pentaquine: (b) for *exo-erythrocytic form*, proguanil, pentaquine and pamaquin and (c) for sexual form, pamaquin.

SUMMARY.—No single drug is satisfactory in vivax infection; quinine or proguanil with pamaquin is so far the best method. For subtertian infection, proguanil is the best, may be combined with quinine or pamaquin. Quinine although cuts short the febrile paroxysm more rapidly than any, it is singly not sufficient for cure.

A SCHEME FOR THE TREATMENT OF MALARIA

The Medical Research Council of Great Britain recommended the following treatment.

(i) *Prophylactic* in the endemic area, paludrine 300 mg. weekly or 100 mg. daily in the malarial season.

(ii) *Therapeutic*: (a) for subtertian infection in a non-immune person, proguanil 300 mg. twice daily for 10 days with mepacrine 300 mg. or quinine 10 gr. t.d. for the first day only: afterwards proguanil 100 mg. daily for six weeks or so long as residing in the endemic area. (b) For a clinical attack in a semi-immune person as local people, a single dose of 300 mg. gives clinical cure. (c) In pernicious attacks, mepacrine intramuscularly or quinine intravenously is required. (d) In vivax infection, proguanil 100 mg. with pamaquine 10 mg. thrice daily for 10 days: in ambulatory cases, a single dose of 300 mg. of proguanil once a week for a year.

(iii) Further, bowels are opened by calomel followed by salts in the febrile stage: an alkaline mixture is given alternating

with quinine or mepacrine : afterwards, during convalescence, anthracenes, usually in pill form, are given with iron and arsenic to keep the bowels regular and cure anæmia.

Non-official Preparations

TINCTURA CINCHONÆ.—Extract of cinchona 10 and alcohol (70%) to make 100. *Standardised* to contain 1% of alkaloids.

Dose, 30 to 60 minims or 2 to 4 ml.

TINCTURA CINCHONÆ COMPOSITA.—Extract of cinchona 50, dried bitter orange peel 50, serpentary 25, cochineal 3 and alcohol (70%) to make 1000. Dose, 30 to 60 minims or 0.2 to 4 ml.

QUININE HYDROBROMIDE and **ACID HYDROBROMIDE**, are given for quinine action in 5 to 10 grs. doses : believed to cause less cinchonism.

ESANOFELE pill has quinine sulph. 2.5 gr., arsenious acid 1/30 gr., citrate of iron $\frac{1}{4}$ gr., strychnine sulphate gr. 1/200 and vegetable bitters q.s. One pill 3 times daily has some reputation in chronic malaria.

QUINOSTOVAR SOL (gr. 4 tablets) given in chronic malaria.

QUININE SALICYLATE, **QUININE ACETYL-SALICYLATE** are used in malaria associated with much pain in the body in 3 to 5 grs. doses, 3 to 4 times daily.

UREA-QUININE HYDROCHLORIDE is used as a local anæsthetic in 2% solution : also made into ointment and suppository (for painful piles).

V. Chemotherapy of Amoebiasis

Drugs included in this group are *emetine*, *carbarsone* and *chiniofon* : recently *chloroquine* (see p. 349) and *aureomycin* are establishing their claims.

IPECACUANHA (*Ipecac.*)

The dried roots or the rhizome and root of *Cephælis Ipecacuanha* of Brazil or *C. acuminata* of Cartagena, Nicaragua or Panama : brought to Europe in 1648. In India it is cultivated in a small scale in the Nilgiris and in Mungpoo.

Root : Brownish grey or dark brown tortuous pieces about 6 inches long and 0.18 in. thick (15 cm. \times 6 mm.) ; closely annulated : ridges rounded and more or less encircling the root. **Rhizome** : short lengths attached to the roots cylindrical about 0.08 in. (2 mm.) in diameter finely wrinkled longitudinally. **Root bark** consists of the thin brown cork layers and a wide parenchyma containing starch and having a bitter taste. These contain 3 alkaloids. These are *Emetine*, *cephæline* and a minute quantity of *psychotrine* : also contain a little tannin.

These should contain not less than 2% of total alkaloids of *Ipecacuanha* calculated as emetine. The alkaloids were isolated by Pelletier in 1817.

Ipecacuanhæ Pulvis (*Ipecac. Pulv.*). See p. 53.

OFFICIAL PREPARATIONS.—(i) **Ipecacuanha Præparata** (*Ipecac. Præp.*). See p. 52. Contains 2% total alkaloids of *Ipecacuanha* root, calculated as emetine. This may be adjusted by adding a little sugar of milk. Dose, $\frac{1}{2}$ to 2 grains or 30 to 120 mg. as expectorant. 15 to 30 grains or 1 to 2 grammes as emetic. (ii) **Extractum Ipecacuanhæ Liquidum** (*Ext. Ipecac. Liq.*). See p. 40. Contain in 2 minims about 1/25 grain of the total alkaloids, about 2%). Dose, $\frac{1}{2}$ to 2 minims or 0.03 to 0.12 ml. (10 to 30 minims or 0.6 to 2 ml. as emetic). (iii) **Pulvis Ipecacuanhæ et Opii** (*Pulv. Ipecac. et Opii*). *Dover's powder* : See p. 53. Contains 1 in 10 of opium and 1 in 10 of *ipecacuanha*. Dose, 5 to 10 grains or 0.3 to

0.6 gramme. (iv) *Tabellæ Ipecacuanhæ et Opii* (*Tab. Ipecac. et Opii*), See p. 57. Morphine content is between 0.9 to 1.1% of the stated amount of powder. Dose, as of powder of Ipecac. and opium. (v) *Tinctura Ipecacuanhæ* (*Tinct. Ipecac.*), See p. 59. Contains 0.1% of the total alkaloids. Dose, 10 to 30 minims or 0.6 to 2 ml. as expectorant and $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. as an emetic. (v) *Trochiscus Morphinæ et Ipecacuanhæ* (*Trochis. Morphin. et Ipecac.*), See p. 61. Each contains $\frac{1}{32}$ gr. of morphine hydrochloride and $\frac{1}{10}$ gr. ipecacuanha.

1. EMETINÆ ET BISMUTHI IODIDUM (*Emet. et. Bism. Iod.*), Emetine and Bismuth Iodide.

A complex iodide, prepared by precipitation from a solution of emetine hydrochloride by the addition of a solution of potassium bismuth iodide. It contains 25 to 29% of emetine and 18 to 22% of bismuth. An orange red inodorous powder with a bitter acrid taste. Insoluble in water and alcohol (95%). Soluble with decomposition in concentrated acids and alkaline solutions. Should be kept in a stoppered phial away from light. It was first prepared by DuMéz. (1915).

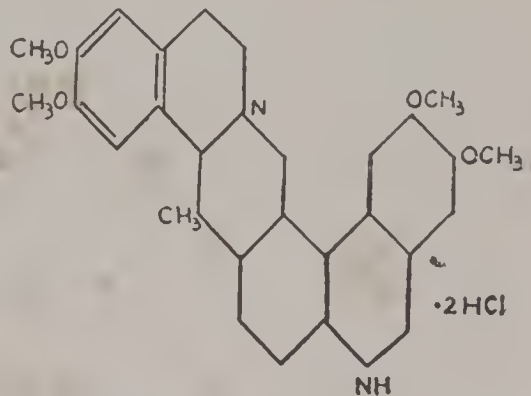
Dose, 1 to 3 grains or 60 to 200 mg. daily.

2. EMETINÆ HYDROCHLORIDUM (*Emet. Hydrochlor.*), Emetine Hydrochloride, $C_{29}H_{40}O_4N_2, 2HCl, 7H_2O$.

Obtained from Ipecacuanha root or prepared by methylation of cephæline. It is a colourless crystalline powder becoming faintly yellow on exposure to light: inodorous with a bitter taste. Freely soluble in water and alcohol (90%). Contains 69 to 74% of emetine. Should be kept in a stoppered phial away from light.

Dose, $\frac{1}{2}$ to 1 grain or 0.03 to 0.06 gramme (30 to 60 mg.) by subcutaneous or intramuscular injection.

Injectio Emetinæ Hydrochloridi.—See p. 43.



Pharmacology [and Therapeutics]

The active substances are cephæline $C_{25}H_{28}N_2(OCH_3)_3(OH)$ and emetine which is methyl-cephæline $C_{25}H_{28}N_2(OCH_3)_3(OCH_3)$: a phenolic group (OH) being replaced by a methoxy group (OCH_3) and are derivatives of isoquinoline. Psychotrine is allied to cephæline but is inert.

Ipecacuanha has a pronounced irritant action on the skin and all mucous surfaces as of the nose, eyes, stomach, intestine and of the bronchioles. These effects are more marked in persons with idiosyncrasy.

ON THE MOUTH, it has an acrid bitter taste and induces a considerable flow of saliva.

ON THE STOMACH, its actions are three-fold according to the dose. (a) *In minute doses* as $\frac{1}{4}$ gr. of the powdered ipecacuanha, it is a *stomachic*³⁵⁶ increasing the gastric secretion. It does not cause any vomiting and may in such doses sometimes even

stop vomiting. [It is prescribed along with other stomachics in some cases of dyspepsia].

(b) *In slightly bigger doses*, it acts on the bronchial mucous membrane through the vagal reflex from the stomach and is an **expectorant**,²⁵⁷⁻²⁶⁰ increasing the bronchial secretion if that is scanty [as in subacute bronchitis]. Ipecacuanha is a mild *diaphoretic* especially when prescribed as Dover's powder.

(c) *In still bigger doses*, as 20 to 30 grains of the powdered root or 1/10 gr. of emetine, it acts as a prompt **emetic**. The action is mainly local, due to gastric irritation and it ceases as soon as the drug is expelled from the stomach. It is a comparatively safe emetic and barring a temporary depression, from the effect of vomiting itself, it has no after-effect.

For this emetic action, powdered root was sometimes prescribed in a case of poisoning also occasionally given to children when there is copious secretion in the bronchioles which they cannot expel by coughing. The act of vomiting squeezes out the secretion from the lungs and gives relief]. This causes depression and is now-a-days seldom resorted to.

SPECIFIC ACTION.—In amœbiasis, emetine is the specific chemotherapeutic agent on **Entamœba histolytica**: the hydrochloride is given subcutaneously in $\frac{1}{2}$ to 1 grain doses daily for 7 days. The vegetative entamœbæ quickly disappear from the stool and the distressing symptoms of the disease are relieved.

Emetine is equally useful in *acute* intestinal and hepatic amœbiasis. In *chronic* and *relapsing* intestinal amœbiasis (those showing cysts only in the stool), carbarsone or chiniofon are more effective.

It is difficult to say how emetine acts. Dobell and Laidlaw (1926) found that emetine hydrochloride 1 in 5,000,000 solution was lethal to *E. histolytica* within 4 days provided the pH of the medium was about 6.4: greater acidity lowered the efficiency. So it appears that for therapeutic purpose, one must aim at maintaining a sufficiently high concentration of emetine at the site of disease consistent with safety also lessening of the acidity

- | | |
|-------------------------------------|---|
| (256) R | Syr. Tolu. min. 20 |
| Ext. Cas. Sagr. gr. 2 | Syr. Scill. ad. min. 60 |
| Ext. Nuc. Vom. Sicc. | Linctus. |
| Ext. Bellad. Sicc. | (259) R |
| Ipecac. Præp. aa. gr. $\frac{1}{2}$ | Tinct. Ipecac. |
| Glycer. Trag. q.s. | Vin. Antim. aa. min. 20 |
| A dinner pill. | Syr. Scill. min. 60 |
| (257) R | Syr. Tolu. ad. fl. oz. 1 |
| Pot. Acet. gr. 20 | Fifteen drops for a child of $\frac{1}{2}$ to |
| Liq. Ammon. Acet. Dil. min. 60 | 1 year in acute bronchitis. |
| Tinct. Ipecac. min. 10 | (260) R |
| Syr. Tolu. min. 60 | Ammon. Chlor. gr. 10 |
| Aq. Camph. ad. fl. oz. 1 | Tinct. Ipecac. min. 10 |
| For acute bronchitis. | Tinct. Scill. min. 15 |
| (258) R | Syr. Tolu. min. 60 |
| Tinct. Ipecac. min. 5 | Inf. Seneg. Rec. ad. fl. oz. 1 |
| Sp. Anis. min. 4 | For chronic bronchitis. |

of the colon by administering kaolin or bismuth carbonate and the action on the entamœbæ is *probably direct* assisted by the natural defence of the tissues of the host.

Emetine, given either subcutaneously or intramuscularly in therapeutic doses, seldom causes any gastric irritation and vomiting and is therefore without any definite action on the respiratory passages also. But with bigger doses, emetine being excreted into the gastro-intestinal tract causes marked inflammation of the mucous membrane of the stomach and intestine resulting in vomiting and diarrhœa. A still bigger dose in animal experiment has been found to cause hæmorrhagic gastro-enteritis and myocardial degeneration.

ON THE CIRCULATION.—Given by the mouth, Ipecacuanha does not produce any definite action as the drug is expelled before it can be absorbed in sufficient quantity. But given hypodermically as emetine, for several days, on account of cumulative action, it causes symptoms of poisoning. Usually 6 to 9 injections of one grain each or less are given followed by an interval of one week and then shorter course of 3 injections with weekly intervals. Intravenous injection of emetine is not necessary except in fulminating cases threatening colonic gangrene. In them, only $\frac{1}{2}$ gr. should be the dose in glucose solution which may be repeated 12 hours after. Later on, only subcutaneous injections are given. Emetine is believed to be useful in capillary hæmorrhage from internal organs and is sometimes given hypodermically in $\frac{1}{2}$ gr. doses for hæmoptysis.

EXCRETION.—Emetine is eliminated mainly by the bowels and slightly by the kidneys. If in some cases, the kidney elimination is greater, emetine does not show as intensive curative effect on the *E. histolytica* in the intestine.

TOXIC EFFECTS.—Although has a high chemotherapeutic action, one gramme being the fatal dose for a human being, at least 15 times of the therapeutic dose, prolonged administration of emetine causes cumulative poisoning which may occasionally appear even after the 4th to 6th injection of one grain each. These are muscular weakness, lassitude, inability for prolonged mental or physical exertion, palpitation, low blood pressure, cardiac arrhythmia and a feeling of faintness: also loss of appetite, nausea, vomiting, abdominal pain and diarrhœa: less commonly, albuminuria, general œdema, petechial hæmorrhages, urticaria, hæmoptysis and polyneuritis. Sudden collapse with heart failure is also known. So the dose, interval and the physical condition of the patient should be carefully assayed if prolonged administration is required. The patient should preferably be *kept in bed* during the period of treatment. Given with due precautions, pregnancy is no contraindication.

In rabbits died of fatal emetine poisoning, degenerative changes of the heart muscles and also hæmorrhagic inflammation of the alimentary tract are found.

Treatment.—Further administration of emetine must be stopped and symptomatic supportive treatment undertaken.

Emetine Bismuth Iodide.—It is given orally in chronic amœbiasis, often indicated by the presence of amœbic cysts in the stools, in 2 to 3 grs. doses daily at bed-time for 10 to 15

nights²⁶¹⁻²⁶². A dose of chlorbutol may also be necessary beforehand to prevent vomiting. This insoluble preparation passes through the stomach nearly unchanged and liberates emetine in the small intestine. It is sometimes helpful in many chronic resistant and relapsing cases.

The *advantage* of emetine bismuth iodide and other amœbiocidal preparations orally is that the drug reaches the site of the disease in the intestine directly. In chronic cases, where on account of long standing ulcerative processes in the intestine much scarring has taken place and the blood vessels are comparatively few, emetine given hypodermically does not sufficiently concentrate there and the therapeutic effect is consequently poor. To such cases, the drugs suitable for oral administration are more effective but these are of less value when the infection is localised outside the alimentary canal e.g. in the liver (amœbic hepatitis). E.B.I. is best prescribed in gelatin capsules.

The *disadvantages* are, (i) nausea and vomiting may be troublesome in some cases ; (ii) the liberated emetine may cause diarrhœa, colitis and even intestinal hæmorrhage. (iii) Sometimes cardiovascular depression may follow.

Carbarsone, chiniofon and vioform have largely replaced emetine bismuth iodide.

Non-official Preparations

HOLARRHENA ANTI-DYSENTERICA (*Kurchi*).—Its bark and seeds are used for the treatment of subacute and chronic dysenteries. Its use has been mentioned in Charaka (nearly 1000 B.C.).

Its active principles are several alkaloids, the most important of which is *conessine*, some gum-resins, tannin, etc. The alkaloids go by the common name of *Kurchi* alkaloids and these have been found to be effective in milder *Entamœba histolytica* infection.

IND. PHARM. LIST PREPARATIONS are (i) KURCHI BARK (*Dose*, 8 to 15 grains or 0.5 to 1 g.).

(ii) EXTRACTUM KURCHI LIQUIDUM, containing 1% of the alkaloids (*Dose*, 180 to 240 min. or 12 to 16 ml.) and (iii) KURCHI ET BISMUTHI IODIDI, *Dose*, 5 to 10 grain or 0.3 to 0.6 g.).

We have made a thorough investigation of their therapeutic possibilities and introduced for the *first time* (1927)* a standardised alcoholic extract containing 1% of the alkaloids now extensively used. Our conclusions are as follows :—The *advantages* are, (i) these are not nauseating and so can be given by the mouth. (ii) These are non-toxic and non-cumulative and so may be taken for a long time without interval and are easily excreted by the kidneys. The *disadvantages* are (i) compared with emetine, their action is slower and less powerful. (ii) If the bowels are acting frequently, these are likely to be thrown out and fail to act. (iii) These are not very

(261) R
Emet. et Bism. Iod. gr. 3
Put up in gelatin capsules.
For chronic amœbiasis.

(262) R
Emet. et Bism. Iod. gr. 3
Paraff. Liq. fl. oz. $\frac{1}{2}$ (Jepps)
For chronic amœbiasis.

* (*Advance Therapy*, 1928. *Ind. Med. Gaz.*, 1930. *Journ. of Trop. Med. and Hyg.* London, 1931).

effective intravenously or intramuscularly (apart from pain that may be caused by the i.m. injection), because these are *readily excreted in the urine* and so fail to concentrate sufficiently at the site of infection. (iv) Tablets are often passed out entire with the stools in the acute stage. v) Soluble preparations are so well-tolerated that no case has been made out for using an insoluble compound like Kurchi-bismuth iodide (much worse is keratin coated tablets) obviously an imitation of emetine bismuth iodide where insolubility is purposive to prevent local action of emetine on the stomach.

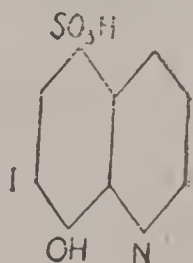
In acute cases, a combination of emetine hypodermically and Kurchi alkaloids by the mouth^{257, 258} gives better result.

CHINIOFONUM (*Chiniofon.*), Pulvis Chiniofoni

Chiniofon, *Quinoxyl* or *Yatren* is a mixture of approximately 4 parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part by weight of sodium bicarbonate. It contains between 27.5 to 29.6% of iodine and between 18 to 22% of NaHCO₃. It was first introduced by Muhlens and Menk (1921).

A light yellow inodorous powder with a bitter, afterwards sweetish taste : soluble with effervescence in about 25 parts of water, insoluble in alcohol (95%), solvent ether and in chloroform.

Dose, 1 to 8 grains or 60 to 500 mg. orally : 15 to 75 grains or 1 to 5 grammes per rectum. The solution is decomposed by boiling.



Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, like many other iodine preparations, it is an **antiseptic** [and in 2 to 3% solution is occasionally used as gargle, vaginal and bladder wash and for dressing surgical wounds].

INTERNALLY, it is more commonly used for the treatment of subacute or chronic **intestinal amœbiasis**. (i) *Orally* it is given in pill form, may be enteric coated, (0.25 gm. or 4 grains each). [First day, one pill is given 3 times daily. From the second to the fifth day, 2 pills and if well tolerated, on the 6th and the 7th day, 3 pills, 3 times daily. With an interval of 4 to 6 days between, 3 courses are usually given]. Chiniofon increases the intestinal peristalsis and may cause diarrhoea with colicky pain for which in some cases, it has to be given in smaller doses as one pill only t.d. or temporarily stopped.

(ii) It is given by *retention enema* also ; starting with 0.5% solution of 300 to 600 c.c., the strength may be increased to 5% if tolerated, daily for one to two weeks. This may be repeated periodically.

(263) R
Kaolin. gr. 60
Mucil. Trag. q.s.
Ext. Kurchi Liq. min. 120
Syr. Aurant. min. 60
Aq. Cinnam. ad. fl. oz. 1
For intestinal amœbiasis.

(264) R
Bism. Carb. gr. 60
Mucil. Trag. q.s.
Ext. Kurchi Liq. min. 120
Glucos. Liq. min. 60
Aq. Chlorof. ad. fl. oz. 1
For intestinal amœbiasis.

The result in chronic cases especially in those resisting emetine treatment, is often very good. Sometimes oral and rectal administrations of chiniofon are combined following emetine injections.

So while emetine is the drug of choice in the acute stage, in the chronic, relapsing and in resistant cases, chiniofon answers better; in fact some observers, especially Craig think that chiniofon is the best amoebicide. Toxicity is also less than that of emetine or carbarsone.

Yatren casein combination (3% of former and 2.5 to 5% of the latter), has been found useful in non-specific shock-therapy in various sub-acute or chronic inflammatory processes in 0.2 to 5 c.c. doses intramuscularly or intravenously.

Non-official Preparations

VIOFORM, *Iodochlorhydroxyquinoline*, an insoluble greyish powder, given in capsule of 0.25 gm. (4 grains), 3 or 4 times daily for 10 days and may be repeated after an interval for 10 days. This has the same action as of Yatren and some observers consider it to be better. Other commercial names are *Enterokinol*, *Quinambicide* and *Enterochin*. Also *Quiniochlorum*. IND. PHARM. LIST.

ENTERO-VIOFORM, Vioform with sapamin which enhances the dispersion of the drug in the intestine, is more frequently used.

DIDOQUIN (5.7-diiodo-8 hydroxyquinoline) and **EMBEQUIN** in 3.2 gr. tablets 3 tablets, t.d. for 20 days has been found useful.

Unlike chiniofon which is poorly absorbed, both vioform and diodoquin are absorbed into the blood and are useful in deep-seated amoebiasis. **CHLOROQUINE** is so readily absorbed that it is more effective in amoebic hepatitis than in intestinal affection (p. 349): given in 0.25 g. tablets 4 times daily for 2 days and then twice daily for 3 to 4 weeks.

A SCHEME FOR THE TREATMENT OF AMOEBIASIS.

(i) In the acute stage injections of emetine hydrochloride, $\frac{1}{2}$ to 1 grain are given daily for 6 to 9 days. Two or three short courses of three injections each may be given at weekly intervals afterwards. Along with this, 60 grs. of colloidal kaolin and 120 minims of 1% liquid extract of Kurchi flavoured with syrup and chloroform water are given 3 times daily for one month. Undue constipation is prevented by castor oil or liquid paraffin emulsions.

(ii) For amoebiasis outside the alimentary canal, emetine injections or chloroquine orally are effective.

Emetine is to be repeated periodically in courses of 3 injections fortnightly, during the subacute stage of the disease.

(iii) In subacute or chronic dysentery also in acute cases when active symptoms have subsided, courses of insoluble emetine preparations, carbarsone, chiniofon (orally and rectally), enterovioform and acetarsol are required with intervals. Other drugs occasionally prescribed are diodoquin, embaquin or diodoxylin.

(iv) Amœbiasis is a chronic infective process and if the scarring of the intestine is great, the entamœbæ make fortified nests for them in the scar tissue and are not much effected by emetine injections : in such cases, the oral and rectal medications of chiniofon, diodoquin and carbarsone are more helpful.

(v) All amœbicides, except Kurchi alkaloids, are toxic and cannot be administered uninterruptedly long enough and intervals must be given. During such periods, the treatment is kept up by the Kurchi alkaloids either in mixture or in tablets of the total alkaloids in a soluble form.

(vi) Earlier the specific treatment is started and carried on in a comprehensive manner (avoiding the toxic action of the drugs also), greater is the chance for complete cure : an insufficient or a slipshod treatment results in complications, carrier state (which may be lasting nearly life long) or chronic emetine or arsenic poisoning.

(vii) In certain cases, streptococcal infection of the ulcers is responsible for failure of the amœbicides and some of these cases may have fulminating symptoms. They are given penicillin 1 lac units followed by 33,000 units every 3 hrs. intramuscularly till 10 lacs are given : also sulphasuxidine 5 g. every 4 hours till 60 g. Next, the amœbicides are given as outlined above. (Hagreaves, 1945).

VI. Chemotherapy of Bacterial Infections

The bacterial infections were so long remarkably resistant to chemical drug treatment. No substantially successful advance was made till the introduction of the *Sulphonamides* followed by the *antibiotics*. Their number is progressively increasing. *Para-amino-salicylate* and *Sulphetrone* are recently introduced.

1. Sulphonamides

These are compounds of *sulphonic acid* and *amides*. The first compound of the sulphonamides of therapeutic use is probably chloralamine which is derived from *p*-toluenesulphonamide by the replacement of the two hydrogen atoms in the amide group by an atom each of sodium and chlorine. Sulphanilamide was prepared in 1908 by Gelmo and sulphonamide dyes in 1909 : these were used as colouring agent. Although German and American workers were investigating their bactericidal action (Heidelberger and Jacobs, 1919), not much advance was made till *red prontosil* was prepared in 1932 (Klarer and Metzsch) and in 1933, its clinical effects of curing acute peritonitis in a boy was described (Foerster). Early in 1935, Domagk published his experimental reports carried on since 1932 which immediately caused world-wide interest and red prontosil was accepted as of undoubted curative value for streptococcal infection.

It was also found that the simpler compound *p*-aminobenzene sulphonamide, more often called *sulphanilamide* is equally effective. The success attained, stimulated further researches and of the many compounds, sulphanilamide, sulphapyridine, sulphacetamide, sulphathiazole, succinylsulphathiazole, phthalylsulphathiazole, sulphadiazine and sulphamerazine have attained outstanding success in many bacterial infections.

The parent substance sulphanilamide, $C_6H_4SO_2NH_2.NH_2$ has SO_2NH_2 , the sulphonamide group and NH_2 , the amino group in the benzene ring. But it was soon found that sulphanilamide although effective in streptococcal infection, is nearly inactive in many other infections and has toxic properties. Newer compounds allied to it but more effective against many other infections and less toxic were prepared. These were made by linking with sulphanilamide various other compounds.

The toxicity often depends on the rate of absorption: those which are readily absorbed cause more powerful effect on the bacteria circulating in the blood and are more toxic also: those which are not as readily absorbed cause more marked local bactericidal effect on the intestine and are less toxic to the host.

1. SULPHANILAMIDUM (*Sulphanilamid.*), *p*-aminobenzene sulphonamide, $C_6H_4O_2N_2S$.



This is prepared by hydrolysis of the amide of acetyl sulphanilic acid with hydrochloric acid, followed by decomposition of the resulting hydrochloride with alkali. It should contain between 99 to 100.5% of $C_6H_4O_2N_2S$, the substance dried in vacuo at 100° .

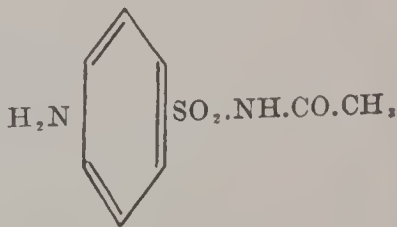
Colourless crystals or white crystalline inodorous powder with slightly bitter taste and sweet after taste. Soluble at 15.5° in 250 parts of water: sparingly soluble in alcohol.

DOSE, the *initial*, 30 grains or 2 grammes followed by 15 grains or 1 gramme every four hours.

Tabellæ Sulphanilamidi (*Tab. Sulphanilamid.*), See p. 58.

2. SULPHACETAMIDUM (*Sulphacetamid.*), Albucid
 $NH_2.C_6H_4.SO_2.NH.COCH_3$.

Para-aminobenzene sulphonacetamide is prepared by acetylation of sulphanilamide with acetic anhydride followed by hydrolysis of one acetyl group. It has an acetyl group in the SO_2NH_2 side chain rather than in the NH_2 group. It should contain not less than 99% of $C_8H_{10}O_3N_2S$, the substance dried at 100° .



A white or yellowish-white crystalline powder, inodorous and acid and slightly saline taste: soluble at 20° in 150 parts of water. In mineral acids and in solutions of alkali carbonates: soluble in 15 parts of alcohol (95%) and insoluble in solvent ether.

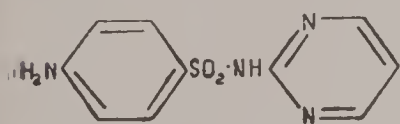
DOSE, (Not official), 30 gr. or 2 g. initially and 15 gr. or 1 g. every 4 hours afterwards.

3. SULPHACETAMIDUM SODIUM (*Sulphacetamid. Sod.*), $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NNaCOCH}_3\text{H}_2\text{O}$.

Sodium para-aminobenzene sulphonacetamide is prepared by adding alcohol to a strong aqueous solution prepared by adding sodium hydroxide solution to molecular equivalent of sulphacetamide in aqueous suspension. This should contain not less than 99% of $\text{C}_8\text{H}_9\text{O}_3\text{N}_2\text{SNa}$.

A white or yellowish white microcrystalline powder, inodorous with slightly bitter taste : soluble in 1·5 of water, sparingly in alcohol (95%).

4. SULPHADIAZINA (*Sulphadiazin.*), $\text{C}_{10}\text{H}_{10}\text{O}_2\text{N}_4\text{S}$.



This is 2-(*p*-aminobenzene sulphonamide)-pyrimidine, prepared by condensation of *p*-acetamidobenzenesulphonyl chloride with 2-aminopyrimidine, followed by hydrolysis of the acetyl group by

heating with aqueous sodium hydroxide solution. Has a pyrimidine nucleus attached to sulphanilamide. It should contain not less than 99% of $\text{C}_{10}\text{H}_{10}\text{O}_2\text{N}_4\text{S}$, dried at 100°.

A white or yellowish white powder, slowly darkening on exposure to light. Almost odourless and tasteless. Soluble at 25°, in about 13,000 parts of water : sparingly soluble in alcohol (95%) and readily soluble in dilute mineral acids and watery solution of alkali hydroxides.

Dose, 30 grains or 2 gramme *initially* and 15 grains or one gramme every 4 hours afterwards.

5. SULPHADIAZINA SODIUM (*Sulphadiazin. Sod.*), $\text{C}_{10}\text{H}_9\text{O}_2\text{N}_4\text{SNa}$.

This is the sodium salt of the above and prepared by its interaction with sodium hydroxide.

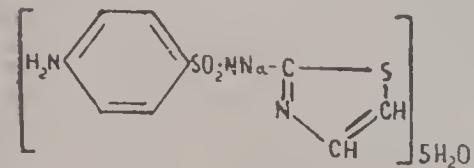
A white or yellowish white, inodorous and nearly tasteless powder, soluble in 2 parts of water at 25°, sparingly soluble in alcohol (95%). It contains not less than 99% of $\text{C}_{10}\text{H}_9\text{O}_2\text{N}_4\text{SNa}$ dried at 105° for 4 hours.

Dose, 30 grains or 2 grammes *initially* and 15 grains or 1 gramme every 4 hrs. afterwards : intravenously 8 to 30 grains or 0·5 to 2 grammes.

Injectio Sulphadiazinæ Sodii (*Inj. Sulphadiazin. Sod.*), See p. 47. Contains 85 to 105% of Sodium sulphadiazine of quantity stated in the label.

Dose as of Sodium sulphadiazine : if the strength is not stated, one containing 15 gr. in 150 min. or 1 g. in 10 ml. is dispensed.

6. SULPHATHIAZOLUM SODIUM (*Sulphathiazol. Sod.*), $\text{C}_9\text{H}_8\text{O}_2\text{N}_3\text{S}_2\text{Na}5\text{H}_2\text{O}$.



Soluble sulphathiazole or Sodium sulphathiazole is the pentahydrate of the Sodium derivative of 2-(*p*-aminobenzene sulphonamide)-thiazole and obtained by interaction of this substance with Sodium hydroxide. It contains not less than 99% of $\text{C}_9\text{H}_8\text{O}_2\text{N}_3\text{S}_2\text{Na}$ dried at 100°.

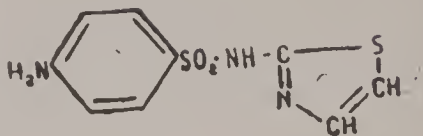
A white or yellowish white micro-crystalline inodorous and nearly tasteless powder, soluble at 15·5° in about 3 parts of water and 20 parts of alcohol 95%. Dose, 30 grains or 2 grammes *initially* and 15 grains or 1 gramme every 4 hours afterwards.

Injectio Sulphathiazoli Sodii (*Inj. Sulphathiazol. Sod.*), See p. 47. Contains 95 to 105% of the amount stated in the label.

Dose as of soluble sulphathiazole intravenously.

7. SULPHATHIAZOLUM (*Sulphathiazol.*), Thiazamide and Cibazol, $C_9H_9O_2N_3S_2$.

This is 2-(*p*-aminobenzene sulphonamide).thiazole, prepared by condensation of *p*-acetamidobenzene sulphonyl chloride with 2-aminothiazole, followed by hydrolysis of acetyl group by heating with dilute hydrochloric acid or caustic soda solution. It should contain not less than 99% of $C_9H_9O_2N_3S_2$, the substance being dried at 100° . This is the first compound to contain a thiazole ring substituted in the sulphonamide side chain.

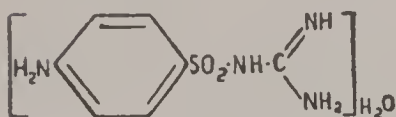


White or yellowish white inodorous, nearly tasteless powder, soluble in 2500 parts of water and freely in dilute mineral acid or alkali hydroxide solution.

Dose, 30 grains or 2 grammes *initially* and 15 grains or 1 gramme every 4 hours afterwards.

Tabellæ Sulphathiazoli (*Tab. Sulphathiazol.*), See p. 58.

8. SULPHAGUANIDINA (*Sulphaguanidin.*), $C_7H_{10}O_2N_4S.H_2O$.



This is *p*-aminobenzene-sulphonylguanidine-mono-hydrate prepared by the fusion of dicyandiamide with *p*-aminobenzene sulphonamide containing not less than 99% of $C_7H_{10}O_2N_4S$ dried at 110° for four

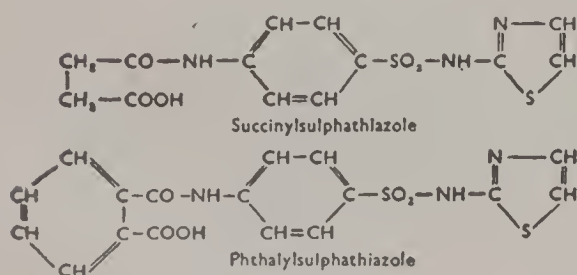
hours. This is a combination of Sulphanilamide and guanidine.

A white needle-like crystalline powder, slowly darkening on exposure to light, almost inodorous and tasteless. Soluble in about 1000 parts of water at 25° : sparingly soluble in alcohol and readily soluble in dilute mineral acids but insoluble in alkali hydroxides in aqueous solution.

Dose, 30 to 60 grains or 2 to 4 grammes.

Tabellæ Sulphaguanidinæ (*Tab. Sulphaguanidin.*), See p. 58.

9. SUCCINYLSULPHATHIAZOLUM (*Succinylsulphathiazol.*), $C_{13}H_{13}O_5N_3S_2.H_2O$.



Succinylsulphathiazole is *p*-2'sulphonthiazolylamido succinilic acid, prepared by condensing sulphathiazole with succinic acid: contains not less than 99% of $C_{13}H_{13}O_5N_3S_2$, the substance dried at 105° .

A white or yellowish white inodorous crystalline powder, slowly darkening on exposure

to light nearly insoluble in water and alcohol 95% but soluble in alkali hydroxides in water and in sodium bicarbonate solution.

Dose, 45 to 90 grains or 3 to 6 grammes.

Tabellæ Succinyl Sulphathiazoli (*Tab. Succinyl Sulphathiazol.*) (See p. 58.

All Sulpha drugs are to be kept in well closed container, protected from light.

Pharmacology [and Therapeutics]

The drugs of the sulphonamide group are used for their antibacterial effect by *inhibiting multiplication of bacteria* in (a) the systemic circulation, (b) urinary tract and (c) in the intestinal canal. For the first, sulphanilamide, sulphathiazole, sulphadiazine and sulphamerazine: for the second, some of

these and sometimes sulphacetamide and for the last, sulphaguanidine, succinylsulphathizole and phthalylsulphathiazole are usually used.

Sulphanilamide came into clinical use in 1937, sulphapyridine in 1939, sulphathiazole in 1940, sulphadiazine in 1941 and the rest followed after.

1. **SULPHANILAMIDE**, given orally in therapeutic doses is pharmacologically more or less **inert** but has been found to be a highly **powerful chemotherapeutic agent** against *betahæmolytic streptococci*. This is less active in *streptococcus viridis* infection. It has no action on enterococci.

It is moderately successful in *B. coli* infection especially of the urinary tract also to some extent in *gonococcic* and *meningococcic*, less so in *staphylococcic* and *pneumococcic* infections. It is also effective in *gas gangrene infection* by Welch bacilli, (sulphathiazole and sulphadiazine are more potent) and to a less extent in brucella infection. Of the virus diseases, it is of value in *lymphogranuloma inguinale* (climatic bubo) and in *chancroid*. It is also prescribed in *trachoma*.

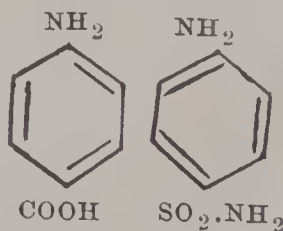
It is of *prophylactic* value if administered before an operation or immediately following a crushing injury. It may be *applied locally* on the wound surface; this has marked therapeutic effect.

The action especially evident in an acute infection, may be (a) **bacteriostatic**, stopping further growth of the organisms or/and (b) **bactericidal**, killing the susceptible bacteria. Of these, the first effect is more marked in most cases but there is no evidence that bacterial toxin is neutralised. In addition, (c) **the response of the host** to the infection is an important factor which varies in individuals also in different types of infection.

MODE OF ACTION.—How the drug acts on the bacteria is not definitely known. There is no obvious systemic leucocytosis: on the contrary, there is a risk of lessening of the polymorphonuclear cells (agranulocytosis) although some local phagocytosis takes place. The specific immune bodies in the blood are also not definitely increased.

It is believed that *p*-aminobenzoic acid (P.A.B.A.) is an essential metabolite for bacterial growth. *P*-aminobenzene

sulphonamide in optimal concentration displaces this (p. 11) and combines with the enzyme system of bacteria and as a result the bacteria fail to multiply for want of nourishment. But if sulphonamide is insufficient in quantity or pus is present which supplies *p*-aminobenzoic acid, bacterial growth is not interfered with. For the same reason, local anæsthetics like procaine (another *p*-aminobenzoic acid compound) also interferes with sulphonamide action.



PABA Sulphanilamide

The clinical result suggests that the drug inhibits the growth and invasive power of bacteria to such an extent that the humoral and cellular defences of the body can cope with the infection and cause final sterilisation. The administration is compatible with simultaneous serum or penicillin therapy. Pus if present must be evacuated as this lessens the activity of sulphonamide.

ABSORPTION AND ELIMINATION.—Administered orally, it is poorly absorbed from the stomach but is readily absorbed from the small intestine, a tablet within four hours and if in solution, in one hour. It is readily absorbed if injected subcutaneously or intramuscularly in a soluble form but does not cause more concentration in the blood than what follows the oral administration and is excreted by the kidneys more readily.

It diffuses readily in all tissues except fat and bone and to a less extent, in nerve tissues without selective fixation reaching nearly the same concentration as in blood. It is present in the saliva, in secretions of the stomach, intestine and pancreas, bile, milk, sweat and tears. It collects in various exudates and transudates and in the cerebrospinal fluid in a concentration 10 to 25% below the blood : in the urine, on 10 to 20% higher level.

It circulates in the blood partly in free state and partly conjugated (acetylated) being made into acetyl sulphanilamide probably by the liver. This is inert on the bacteria, but as toxic as the original sulphonamide to the host. Being not very soluble tends to block the renal tubules.

About 20% of sulphanilamide, 35% of sulphapyridine, 10% of sulphadiazine and 20% of sulphathiazole are acetylated in blood.

The excretion is quick, mainly through the urine making up 90 to 95% as sulphanilamide and acetyl sulphanilamide : their proportion varies from time to time.

PRECAUTIONS.—Disturbed condition of the alimentary system as vomiting, diarrhoea or constipation alters the rate of absorption. A single dose of 0.1 gram. per kg. body weight gives a concentration in blood near about 10 mg.%. About 10 to 12 mg.% and in very severe infection, up to 15 mg.% is the *therapeutic blood concentration* and this must be maintained. The elimination is nearly complete in four hours and after an initial big dose, this drug is repeated in smaller doses every four hours to maintain the concentration reached in the blood. Treatment with an adequate dose and for a sufficiently long period is essential for effective therapy : further any pus pocket if present must be evacuated. If these are not done the bacteria escape destruction and may even become drug fast.

The functional efficiency of the *kidneys* is also a regulating factor. During excretion through the kidneys the drug attains a higher concentration there than in the blood and the therapeutic activities are manifested best there and it is the most

powerful **urinary disinfectant** ; for the same reason it should not be given if renal disease is already present especially any acute renal affections. Further, as this in acetylated form is less soluble, this is readily precipitated in the renal parenchyma (*sulphonamide crystalluria*) and cause renal irritation and even formation of calculi and tubal block.

Solubility of Sulphanilamide in 100 c.c. of water at 37°C, is 1460 mg. : Sulphathiazole, 32 mg. : of Sulphapyridine 49 mg. : Sulphamerazine 32 mg. and Sulphadiazine 13 mg. With pH 7.5 the solubility is altered as follows : Sulphathiazole 235 mg. and acetylsulphathiazole 28 mg. : sulphadiazine 200 mg. and acetylsulphadiazine 512 mg. : Sulphamerazine 170 mg. and acetylsulphamerazine 272 mg. per 100 c.c. of the fluid

So in therapeutic administration of these, simultaneous administration of *alkalies* as sodium bicarbonate increases solubility, rate of absorption and ionisation and lessens possibilities of retention, crystalluria and other toxic manifestations. For this 15.6 g. of Sod. bicarb. (40 gr. every 4 hours) and 1500 c.c. of fluid must be taken daily, these being necessary to flush out the precipitated acetylated crystals if any.

COMBINATION OF SULPHONAMIDES.—Usual daily dose for systemic action has been taken to be 6 g. If a mixture of sulphathiazole, sulphadiazine and sulphamerazine are given in nearly equal parts, (about 2 g.) bactericidal effects would be the same as of one given in 6 g. dose. A dose of 2 g. of any of these *will not cause crystalluria* even without alkalies and a combination as stated above is nearly as safe and if given with alkalies is safer still. (Lehr, 1946 and 1947).

Gombisul and *Sulphatriad* are the preparation available commercially in 0.5 gm. tablets : sulphatriad suspension (4 g. in 1 fl. oz.) is for children.

With **local application** of a sulphonamide on a fresh wound, sepsis may be so controlled that primary suturing and closing the wound are often possible. About 0.1 g. of the sterilised sulphanilamide is applied on each square inch, to a maximum of about 10 g. in twenty-four hours : may be combined with penicillin also. Sulphamezathine powder with calcium penicillin 5000 i.u. per g. of powder (Avlon brand) is available.

THERAPEUTIC DOSE for systemic action depends on the intensity of the infection. For a *systemic infection* sulphathiazole, sulphadiazine or sulphamerazine are more commonly used. In a moderately severe one, 4 tablets (2 gm.) as the initial dose followed by 2 tablets (1 gm.) every 4 hours *orally* are necessary. Sodium bicarbonate 40 grains is given along with each dose. If oral intake or absorption is insufficient or the infection is very severe, a soluble preparation as sodium sulphadiazine and sodium sulphathiazole by intramuscular or intravenous drip injection is necessary and the total dose should be for an adult about 6 gm. daily for the first two days and 4 gm. for the next 4 or 5 days. The clinical improvement is apparent in

2 days but the treatment has to be kept up for a few days more. Sulphanilamide and Sulphapyridine are now replaced by less toxic and more effective newer compounds.

TOXICITY.—Considering the large varieties of cases receiving sulphonamide treatment, the toxic symptoms are comparatively rare. In fact in therapeutic doses, the drug is more or less inert on the vital organs. Sulphanilamide and sulphapyridine are more liable to cause toxic manifestations: sulphathiazole is less toxic: sulphadiazine, sulphamerazine, sulphaguanidine and succinylsulphathiazole seldom cause toxic symptoms. Acute toxic effects are uncommon: chronic poisoning may follow repeated administration causing cumulative effects.

SYMPTOMS.—Rise in temperature, giddiness, dizziness, malaise, anorexia, nausea, vomiting, diarrhoea, renal irritation by precipitated sulphanilamide (sulphonamide crystalluria) causing dysuria, hæmaturia and rarely anuria and cyanosis are sometimes seen: the last may be associated with sulph. or methæmoglobinaemia and prevented by withholding the drugs and food containing sulphur as egg or onion: also saline purgatives which by liquefying the stool, favour absorption of sulphuretted hydrogen. Coal tar preparations should also not be used.

Various skin eruptions as urticaria, morbilliform or maculopapular rashes even exfoliative dermatitis: hepatitis, jaundice, hæmolytic anæmia, leucopenia going to agranulocytosis (if marked, may end fatally), thrombocytopenia, acidosis and rarely neuritis are seen.

2. **SULPHATHIAZOLE** is more effective in *staphylococcic* infection such as furunculosis, carbuncle, cellulitis and septicæmia than other sulphonamides.

It is found to be quite effective in *pneumococcic*, *hæmolytic streptococcic*, *gonococcic* and *meningococcic* infections. It may be used in urinary tract infection by *B. Coli* and *B. Proteus*.

It is rapidly absorbed from oral administration and the peak of concentration in the blood is reached in about 3 hours. It more rapidly disappears also from the blood and is excreted and is conjugated to some extent but one-third greater than that of sulphanilamide. Thus it is somewhat difficult to maintain a steady optimum blood level. Its toxicity is less than of sulphanilamide and is one half of sulphapyridine.

DOSE.—A blood concentration of at least 5 mg.% is necessary for therapeutic purpose. On account of more rapid elimination, a higher dose is necessary than the previous ones. The initial dose is 4 gram. and then 1 gram. 4 hourly, total about 60 gram. being often necessary. In *chancroid*, 4 g. daily for 5 days followed by 2 g. for 10 days was successful. The sodium salt is given intravenously also in slow drip infusion in severer cases for rapid concentration.

Obtained in combination with proflavine 1% as dusting powder or 5% ointment and 10% eye ointments: should not usually be applied for more than a week.

SOLUTHIAZOLE is 20% neutral solution of sulphathiazole in 5 c.c. ampoule (1 g.) or 25 c.c. rubber capped phial, for intravenous injection.

GONAZOL tablets with 0.5 g. of sulphathiazol and 0.015 g. proflavine monohydrochloride are used in gonorrhœa.

FORMOCIBALZIN tablets (combination of cibazol and formaldehyde) are used in intestinal infections.

PRIVINE-CIBAZOL is used as nasal drops in congestive rhinitis.

TOXIC SYMPTOMS.—Nausea, vomiting, dizziness and mental confusion are not very common. Drug fever, skin eruptions, injection of sclera and conjunctiva, renal irritation and moderate leucopenia may result, but on the whole, it is a safer drug.

3. **SULPHACETAMIDE**, *Albucid*, *Sulfocid*, is used for the treatment of *gonorrhœa*. It is rapidly absorbed and excreted and has no cumulative after effects. Its toxicity is also low and renal irritation by sulphonamide crystalluria is almost unknown.

Dose is 4 g. initially and 1 g. every 4 hours afterwards alternately with an alkaline diuretic for seven days, blood concentration of 7 to 10 mg% being produced: after an interval of 8 days another course may be given.

It is also used in *other urinary infections* as by *B. coli* and *staphylococci*.

4. **SULPHACETAMIDE SODIUM** is chiefly used *locally*. In acute conjunctivitis, 10% solution is instilled every two hours and in blepharitis 2.5 to 10% ointment is applied to the lid margin: also used in corneal ulcer. In burns a 10% solution may be applied. A 10% ointment is useful in skin affections especially by *streptococci* and *staphylococci*.

Dermucid a 6% ointment in a varnishing cream (Schering) may be used

5. **SULPHADIAZINE** is slowly absorbed and excreted. In the blood about one-tenth of the drug is acetylated and easily excreted in alkaline urine. Gradually a higher concentration is reached in the blood than with any other sulphonamide. It gets widely distributed in different parts of the body reaching blood concentration of 10 to 15 mg.%. It does not cause much vomiting and is better tolerated. But due precaution against renal irritation must be maintained. Its popularity is increasing and is more commonly used than other sulphonamides.

It is useful in *hæmolytic streptococcal*, *pneumococcal*, *meningococcal*, *gonococcal*, *coliform bacillary* and to a less extent in *staphylococcal* infections also probably in *plague*. In an acute case, rapid blood concentration may be reached by intravenous injection of about 3 g. Penicillin may also be given at the same time.

It has been found to be of *prophylactic* value in persons exposed to an infection as before a major surgical operation.

It is also used for *local condition* in the skin in various forms.

For topical application *cream* (5%), *oculentum* (10%) and *paste* (5%), M. & B. are available.

6. **SULPHAGUANIDINE** is poorly absorbed from the alimentary tract and so is useful in *bowels infections* like acute bacillary dysentery especially in *Shiga* infection. It does not cause much vomiting nor much systemic intoxication.

In cholera it is successful in certain cases: but not as frequently as in acute dysentery. The initial dose may be 4 grm.

followed by 2 grm. every 4 hours. A higher dose than this is not usually necessary.

The acute process often subsides in 2 to 3 days when the dose is lessened and continued for another 3 or 4 days.

When given in big doses, a certain amount may be absorbed and cases of severe systemic intoxication have recently been reported.

As Sulphaguanidine inhibits the bacterial synthesis of vitamin B group in the intestine, it is often necessary to supplement especially if taken fairly long. See p. 292.

7. **SUCCINYLSULPHATHIAZOLE** (*Sulfasuxidine*) appears to be a better intestinal antiseptic than sulphaguanidine. Given by the mouth about 5% is absorbed and excreted by the kidneys. Blood concentration with the stated therapeutic dose is 0.5 to 1 mg.% for sulphathiazole and 1 to 2 mg.% for conjugated sulphathiazole fractions.

It has **specific bacteriostatic** action on *E. coli*; *S. Dysenteriae*, *Paradysenteriae* and *Sonne*: also proteolytic anaerobic bacteria. Clinically it is used as a pre-operative treatment before intestinal operation and also in postoperative treatment: this minimizes the risk of peritoneal involvement. The usual dose is 6 to 8 g. daily in divided doses. It is used in bacillary dysentery and in resistant and fulminating amoebic dysentery (p. 357). The stools become semifluid and practically odourless. Fairly satisfactory results have been obtained in ulcerative colitis and ileitis: also in infantile diarrhoea. A rectal suppository of 3 g. of it with 7 g. of cacao butter is used in proctitis. A 20% cream is used in skin affections. From what little is absorbed and excreted in the urine, *E. Coli* pyelitis resisting other treatment may occasionally be cured.

DRUGS OF CHOICE IN VARIOUS INFECTIONS:

(a) *Sulphathiazole*: Staphylococcal infection (furunculosis, cellulitis, carbuncle, localised septic wounds and osteomyelitis) also pneumococcal, meningococcal and gonococcal infections: fairly effective in *B. Coli* and streptococcal infections: to a less extent in bacillary dysentery.

(b) *Sulphacetamide*: gonococcal infection sometimes *B. coli* infection but more commonly, locally in skin and eye affections.

(c) *Sulphadiazine*: pneumococcal, meningococcal, gonococcal, streptococcal, *B. coli*. and staphylococcal infections. Fairly effective in bacillary dysentery.

(d) *Sulphaguanidine*: bacillary dysentery and to some extent, food poisoning, gastro-enteritis, infantile diarrhoea and cholera.

(e) *Succinylsulphathiazole*: preoperative and postoperative treatment for intestinal bacteriostasis: also bacillary and certain cases of amoebic dysentery and gastro-enteritis.

The following infections are *partially amenable* to sulpha treatment: actinomycosis, pemphigus and undulant fever (sulphanilamide); plague and small-pox (sulphathiazole and sulphadiazine); influenzal meningitis and pneumobacillary infections (sulphapyridine).

The following are *not amenable* to sulpha treatment: enteric fever, tuberculosis, leprosy, tetanus, diphtheria, whooping cough, common cold (and most of the virus infections), scarlatina, rheumatic fever, subacute bacterial endocarditis, enterococcal and *S. fæcalis* infection.

Precautions.—Total white cell count (especially of the granulocytes and hæmoglobin estimation should be done frequently. Toxic symptoms as headache, malaise, nausea, vomiting, drug fever, rapid breathing and scantiness of urine also skin eruptions are indications to be cautious in further administration.

SUMMARY.—The first Sulphonamide group of *antibacterials* was *sulphanilamide*, specific against hæmolytic streptococci and less so in other infections. High systemic toxicity, crystalluria and limited field of activity led to search for and discovery of (i) *sulphathiazole* *sulphadiazine*, *sulphamerazine* and *sulphamezathine*, suitable for both systemic and local infections (also *sulphacetamide*): (ii) for intestinal infection, *sulphaguandine*, *sulphasuxidine* and *phthalylsulphathiazole* (these require vitamin B. complex also) came into use.

Non-official Preparations

PRONTOSIL RUBRUM (original sulpha product). PROSEPTASINE (benzyl sulphonamide), SOLUSEPTASINE (5 c.c. of 10 and 20% solutions, given by *injection*) and *topical* application, UREA SULPHAZIDE (oral or solution for *injection*) are sulphanilamide substitutes.

SULPHAPYRIDINE (M. & B. 693) one time very popular in the treatment of pneumonia, meningitis and streptococcal infection, has been replaced by sulphadiazine, sulphathiazole and sulphamerazine, these being less toxic and more effective.

SULPHAMERAZINE, sulphadimidine, is said to be more readily absorbed from oral administration and excretion being slow, higher blood concentration is more easily reached and maintained than with sulphadiazine: renal disturbances are also less frequent even in acid urine. In pneumonia, c.s. fever, hæmolytic strepto. and coliform bacillary infection, 3 to 6 gram, (initial dose) is followed by 1 gram. every 4 hours. In acute gonorrhœa 1.5 grams. every 8 hours. The sodium salt is given by slow intravenous injection, 2.5 g. in 15 c.c. of 12.5% glucose solution which may be repeated. SULPHAMEZATHINE has similar action: used locally and for systemic action.

PTHALYLSULPHATHIAZOLE, *Thalistatin*, *Thalazole*, *Sulphathalidine* is used for the same purpose as succinylsulphathiazole. Being a better bacteriostatic, half dose is sufficient: initial dose of 0.125 g. per kg. body weight (about 15 tablets for an adult) is followed by 1 to 1.5 g. (2 to 3 tablets) every 4 hours. The stool becomes of thicker consistency which is helpful in dysentery, diarrhœa and in ulcerative colitis.

Other sulphonamide compounds recently introduced are *Gantrisin*, *Elkosin*, *Irgafen* and *Diazil* available in 0.5 g. tablets: may be used for sulphonamide action.

MARFANIL, Sulphamylon or Sulphabenzamine has a methylene group between amino and benzene groups. It is active against gram-positive organisms also some of the gram negative and anærobic organisms. It is more effective when applied locally.

2. Penicillinum (*Penicil.*), Penicillin, $C_9H_{11}O_4SN_2R$

PENICILLIN is the most outstanding discovery as a chemotherapeutic agent, obtained from the extracellular product of a strain of *Penicillium notatum*. Other chemotherapeutic agents have been obtained from similar moulds, bacteria and other lower organisms. All these are called **antibiotics**. After penicillin, the next antibiotic of great promise is STREPTOMYCIN obtained from *Actinomyces griseus*.

Penicillin is the anti-infective acid produced by the growth of *Penicillium notatum* or related organisms under appropriate condition and converted into sodium or calcium salt: non-specific impurities are removed and purified penicillin salt is dried under conditions to ensure sterility and stability.

When pure, *sodium penicillin* is a white powder, crystals, granules or scales. This contains 1538.5 units in 1 mg. (p. 23). Less purified sodium or calcium penicillin is pale yellow to light brown amorphous hygroscopic powder or in masses containing not less than 900 units per mg. Very soluble in water, insoluble in fixed oils and in liquid paraffin.

Dose as determined by the Physician as per need of the patient.

INCOMPATIBILITY.—Penicillin is destroyed by Penicillinase, acids, alkalies, oxidising agents, metals and cysteine also heat near to 52° especially in the presence of moisture. A solution has to be used immediately or stored in a refrigerator.

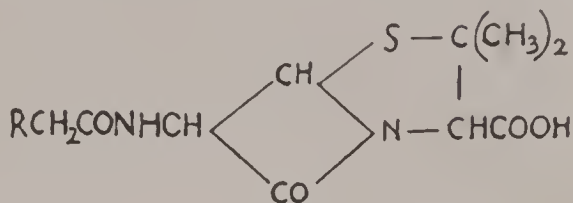
OFFICIAL PREPARATIONS.—(i) *Cremor Penicillini* (*Crem. Penicil.*), Penicillin Cream.—See p. 37. (ii) *Cremor Penicillini Sterilisatus* (*Crem. Penicil. Sterilisat.*), See p. 37. (iii) *Injectio Penicillini* (*Inj. Penicil.*), If several doses are dispensed 0.1% chlorocresol or phenol 0.5% is added. See p. 45. *Strength*, if not stated, is 50,000 units per ml. (iv) *Injectio Penicillini Oleosa* (*Inj. Penicil. Oleos.*), See p. 45. *Strength*, if not stated, is 125,000 units per ml. (v) *Oculentum Penicillini* (*Oculent. Penicil.*), Penicillin eye ointment. See p. 51. *Strength*, if not stated, is 1000 units per g. (vi) *Trochiscus Penicillini* (*Trochis. Penicil.*), Lozenge of penicillin. Each lozenge weighs about 1 g. See p. 61. *Strength*, if not stated, is 500 units per lozenge. (vii) *Unguentum Penicillini* (*Ung. Penicil.*), Penicillin ointment.—See p. 62. *Strength*, if not stated, is 500 units per g.

Pharmacology [and Therapeutics]

HISTORY—In 1929 Fleming found that an area in the culture plate of staphylococci which accidentally was contaminated by a mould, had undergone lysis. By culturing the mould in a nutrient broth, he found that this acquired inhibitory *bactericidal* properties. This property, he found, limited to certain *specific organisms* and the broth culture of it injected into an animal was found to be fairly *non-toxic*. Thus he found the essential specialities of penicillin and laid the foundation of the present remarkable therapeutic achievement. Florey and others several years after purified the product and put into clinical use.

CHEMISTRY.—So far four different penicillins have been obtained (Penicillin and hydropenicillin), in the pure crystalline state. In Britain, these are called I, II, III, and IV in order

of their discovery : in U. S. A., they are called F, G, X and K. These are in aqueous solution strong monobasic acids, readily making salts with alkali metals and earths : dipeptides of a special type possessing a common nucleus but different side chains R. On the whole, penicillin II or G is more commonly used.



R varies in different penicillins. In spite of the apparent simplicity, so far no workable method of synthesis has been obtained. By natural fermentation process in deep vat cultures, penicillin is so readily obtained cheaply that a synthetic preparation will not much improve the situation.

At present the *calcium* and *sodium salts* are used clinically. Recently *potassium penicillin* is also used : it is more heat stable, non-toxic, easily absorbed and the action is comparatively more lasting. It was once thought that the calcium salt had a more harmful effect on the tissues than the sodium salt but this was almost certainly due to impurities : samples have been found quite suitable for parenteral use and local application. Calcium penicillin has the great advantage of being less hygroscopic than the sodium salt.

Since organisms such as *B. proteus* and *Ps. pyocyanea* are not inhibited by penicillin, full aseptic precautions should be taken when the drug is injected or applied locally.

MODE OF ACTION.—Till lately it was believed that penicillin acts on the organisms by causing **bacteriostasis** : the development of the organisms was simply arrested. Now it has been found that on the growing bacteria, penicillin has definite **bactericidal** action (Hobby 1942, confirmed by Bigger 1944). A small percentage of organisms surviving has been found to be in non-dividing phase and penicillin *kills only the bacteria that are about to divide*. It is believed that the respiration of growing bacteria only are affected by preventing oxygen intake, causing their death : bacteria in the resting stage are not affected.

The other suggestion is that penicillin acts by blocking the essential metabolite for the bacteria, glutamic acid. This acid, a component of glutathione, maintains cell metabolism through its sulphydryl group (-SH group) : penicillin dehydrogenates -SH to S-S and as sulphydryl group is not restored, the bacteria die. It is also possible that other enzyme systems may be affected.

Pure penicillin will completely inhibit the growth of the most sensitive organisms such as the gonococcus and staphylococcus, when diluted to at least 1 : 50,000,000, while a preparation less pure will inhibit at 1 : 5,000,000 to 1 : 15,000,000. Penicillin is standardised biologically (p. 23).

One unit is the activity of 0.65 μ g. of crystalline penicillin G : one mega unit is 1,000,000 units.

Unlike sulphonamides, it has no competitive antagonism with *p*-aminobenzoic acid and it is more likely that this as well as sulphonamides show synergistic action with penicillin against Gram-positive cocci.

The antibacterial action of penicillin is *not inhibited* significantly by serum, blood, pus or tissue autolysates, and so it can be used on the most purulent lesions. In addition, the drug is little affected by the number of organisms present.

In general, most Gram-positive organisms especially cocci and some Gram-negative cocci are *sensitive*, and the Gram-negative bacilli *insensitive*, but some species show strain variation. Naturally resistant staphylococci are sometimes encountered, and the streptococcus viridans group sensitivity varies considerably, but no naturally resistant strain of strep. pyogenes has yet been reported.

Organisms sensitive to penicillin are, (i) *Gram-positive cocci* as Staph. aureus (most strains), Staph. albus, Str. pyogenes, Str. viridans (most strains) and D. pneumoniae : (ii) *Neisseriae* as N. gonorrhoeae, N. catarrhalis and N. meningitidis : (iii) *Clostridia* as Cl. welchii, Cl. septicum, Cl. oedematiens and Cl. tetani : (iv) *Viruses* as psittacosis, and ornithosis : (v) *Treponemes* as Trep. pallidum, Trep. recurrentis and Trep. vincenti also Sp. minus : (vi) *Others* are B. anthracis, C. diphtheriae, Actinomyces bovis (some strains) and leptospira icterohæmorrhagiae.

Vibrio El. Tor. and S. gærtneri are *slightly sensitive*, and Ps. pyocyanea, Proteus, B. coli, B. typhosus and paratyphosus, Vibrio cholerae, Strep. faecalis, B. shiga, sonnei and flexneri, H. influenzae, H. pertussis, B. leprae and some strains of staphylococcus, M. tuberculosis, Pasteurella and Brucella are *insensitive*.

ABSORPTION and EXCRETION.—As penicillin is rapidly destroyed by acid of the stomach, it cannot be given orally in the usual way. Penicillin is rapidly *absorbed* from subcutaneous tissues and muscle and passes into the blood stream. It gains access to the pleural and peritoneal cavities, liver, kidneys, intestine, pancreas, heart and lungs. It is *excreted* rapidly and in high concentration in the urine, and is found in the bile and saliva but not in the tears or pancreatic juice. It cannot be detected in the cerebro-spinal fluid after intramuscular or intravenous administration.

THERAPEUTIC ADMINISTRATION.—Penicillin is applied *locally* at the site of the disease if this is within reach and for *systemic action* after absorptions, by injection and occasionally orally.

With *local application*, a continuous concentration must be maintained in contact with all infected tissues. Sloughs and sequestra must be completely removed. Healing can be greatly

hastened by early closure of a wound and instillation of penicillin solution 12-hourly through indwelling tubes. This was successfully done with mastoidectomy wounds, chronic sinuses, osteomyelitis and with compound fractures. Abscesses can be treated by aspirating the pus and injecting penicillin through a needle. The preparations of penicillin used are in powder, solution, cream, lozenges and in ointments.

The cerebrospinal space and the pleural and probably the joint cavities present a special problem in treatment, as penicillin passes only slowly between these cavities and the blood-stream. In meningitis, the intrathecal injection by the lumbar or ventricular route is most effective as a bacteriostatic concentration is usually maintained in the C.S.F. for at least 24 hours. Treatment once a day or even less frequently is sufficient. Similar conditions apply in the treatment of infections in the pleural and joint cavities; for meningitis and arthritis 10,000 units and for empyema 30,000 units daily, along with systemic administration by injections, also sulphonamides orally or/and by injection are helpful.

Infections of the eye and of the skin also offer fields for local application.

SYSTEMIC ADMINISTRATION.—Given by *intramuscular* injection of a watery solution, the peak of blood concentration is reached in 10 to 30 minutes: with a moderate dose of 25000 units, the height reached is about 0.6 units per c.c. of blood serum and disappears from blood in 3 hours. A dose given in beeswax peanut oil suspension or any other repository penicillin, the peak is reached in 6 hours and continues at least for 12 hours. If however a second injection is given at the 8th or 12th hour, a good level is maintained for over 24 hours. Excretion takes place in the urine, about 60% and the rest is metabolized in circulation.

1. LOCAL APPLICATION.

Aerosol therapy.—In disease of the upper respiratory tract inhalation of penicillin mist produced by a special apparatus (p. 18) is sometimes useful. Adult dose may be 25,000 to 50,000 units in one c.c. with isotonic sodium chloride solution.

AVAILABLE as *Penicillin Dispolator* (each inhaler has 100,000 i.u.): *Aerohaler* (each cartridge has 100,000 i.u.): *Penicillin snuff* (5000 i.u. both in lycopodium and lactose base): *Penlator* (a special inhaler).

Eye affections.—Those in the lids, conjunctiva and cornea caused by penicillin-sensitive organisms respond well. Official oculentum for the lid and 2500 units sod. penicillin per c.c. drops or lamellæ frequently applied are useful. As prophylactic in the new born, 2500 i.u. per c.c. drops are used.

AVAILABLE as *Penicillin Ophthalmic discs or tablets* 250 i.u. in each and *Penicillin Eye ointment* 1000 and 25,000 units per g.

Wound surface.—Penicillin is used as (a) solution 250 to 1000 units per c.c. of distilled water or saline : (b) powder 5000 units in sterilised sulphathiazole or sulphamezathine or as (c) cream or ointment of 500 and 1000 units per g. also (d) sterile gauze impregnated with 100 units per g. of the base and 160 units, per sq. inch of the gauze.

For *throat affections* penicillin lozenges, 500 units of calcium penicillin and for *tooth socket* after extraction of the tooth, "dental cone" containing $\frac{1}{2}$ gr. each of sulphamylamide and sulphathiazol and calcium penicillin 1000 units now available.

AVAILABLE as *Penicillin lozenges*. 500 and 5000 i.u. also as *Troches*, 5000, 10,000, 20,000 and 50,000 i.u.

Dental cerate 5000 i.u. each to be put into the cavity after tooth extraction, *Dental tablets* 15,000 i.u. each.

2. ORAL ADMINISTRATION of penicillin is not an ideal method because it is largely destroyed by gastric acidity and the intestine contains penicillinase. Penicillin is sometimes given buffered or with buffer salts as aluminium hydroxide or dihydroxyaminoacetate, sodium citrate, or even without any buffering. But it should be given only on empty stomach, not earlier than $1\frac{1}{2}$ hour after or later than $\frac{1}{2}$ hour before food.

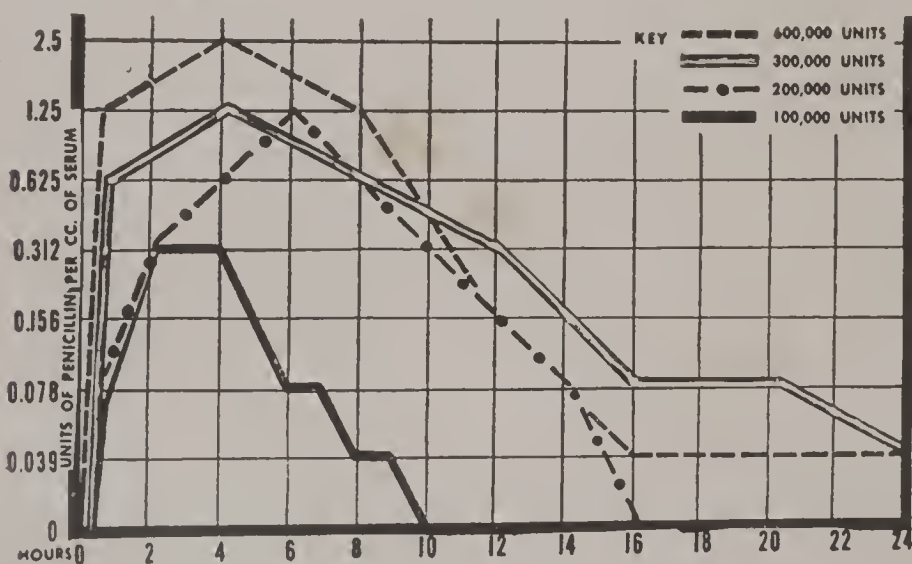


Fig. 18.—Oral administration of buffered Penicillin : effects of different doses are shown on the blood serum

Dose orally should be about 5 times the injected dose : is especially indicated in children, 50,000 i.u. every 3 hours : also in adult may be with an initial good dose by injection, 300,000 i.u. followed by 100,000 i.u. every three hours : successful in pneumonia and gonorrhœa.

AVAILABLE as *Penicillin oral*, sodium or potassium in 50,000, 100,000, 250,000 and 500,000 i.u. tablets. *Gelu-cillin* buffered calcium salt, and *Peni-oral* buffered, have 50,000 and 100,000 i.u. per tablet. *Leder-cillin* *speroid*, chocolate flavoured powder 3 g. having 50,000 i.u. units.

3. PARENTERAL ADMINISTRATION.—*Intramuscular injection* is the ideal method. Given by intravenous injection in watery solution, it is rapidly eliminated in 2 to 2½ hours. It is occasionally given in slow *continuous drip* especially in bacterial endocarditis but the results are not very superior to repeated intramuscular administration.

(i) Often *water-soluble crystalline Penicillin G* is used. The *dose* varies according to the *severity* of the infection and the *susceptibility* of the organisms. In an acute blood infection by a susceptible organism, an adequate blood level of penicillin near about 0.16 units per c.c. is maintained and in a severer or resisting infection, a higher level: more so in less sensitive organisms.

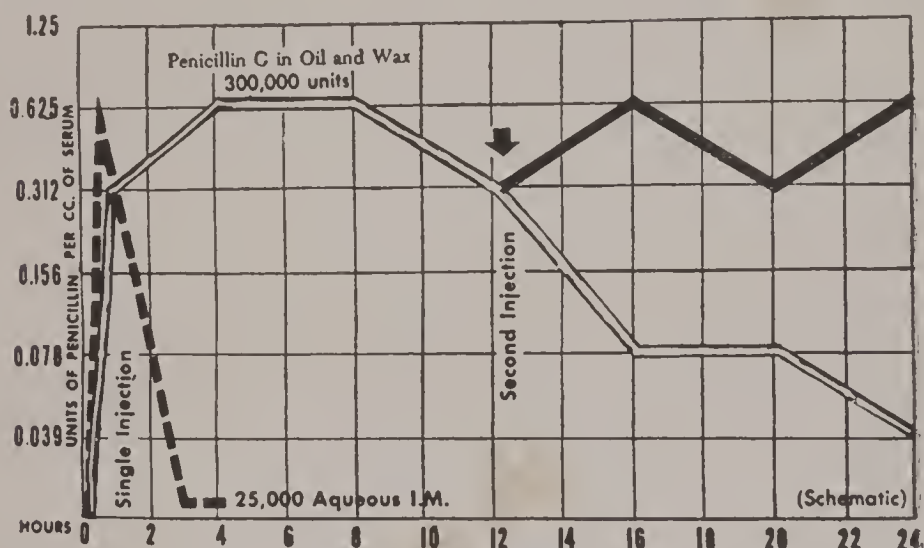


Fig. 19.—The effects of watery solution and of wax and oil suspension of Penicillin on the patient's serum: a second injection in oil and wax causes summation of effect and continuous high serum level.

In a case of moderate severity, 25,000 to 30,000 i.u. in watery or saline solution was given intramuscularly every 3 hours, day and night, till marked clinical effects were produced: a bigger dose as 50,000 units every 3 hours was given in a severe infection: with such a *dose* adequate blood concentration is quickly reached with rapid bactericidal effect: any organisms lurking in a comparatively avascular area may be attacked by over-flow penicillin and more resistant organisms are effectively attacked.

Penicillin now being available more easily and cheaply, tendency is to give it in bigger doses. A *big dose* as 300,000 units keeps up a high blood level for a longer time (about 6 hours) and a high concentration in the tissue exudate for 8 to 18 hours.

This in 2 or 3 daily injections is preferred to many smaller 3 hourly injections: to minimize injections even more, *repository* form of penicillin has been prepared.

(ii) *Wax and oil suspension* minimises the number of injections: 2 injections of 300,000 units daily may do. This will maintain a continuous blood concentration of about 0.6 units per c.c. The disadvantage is difficulty in administration and slow absorption.

(iii) *Procaine penicillin G crystalline* for aqueous injection (a water-insoluble combination of one molecule of penicillin and one molecule of procaine base with one molecule of water of crystallization): this is available in sealed vials in 300,000 and 600,000 units and given once daily: a slow continuous and prolonged blood level is obtained.

(iv) *Procaine penicillin G crystalline with buffered sodium penicillin* for aqueous injection: this has 300,000 units of insoluble and 100,000 units of soluble penicillin: this causes prompt and sustained blood level for at least 24 hours.

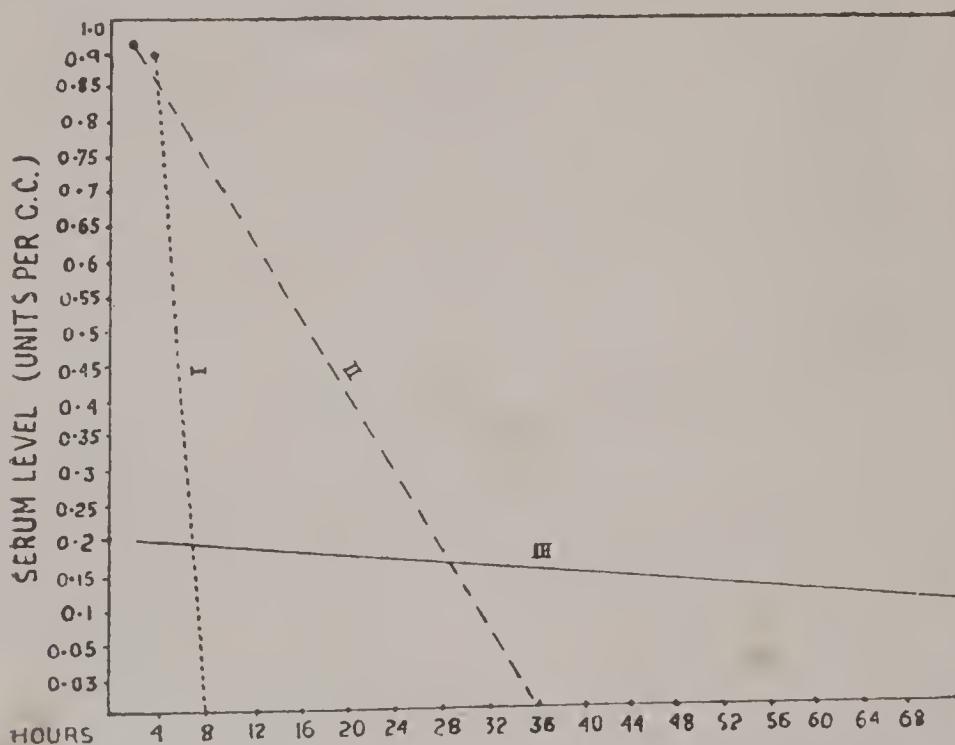


Fig. 20.—Penicillin serum level in units per c.c. reached after one injection of 300,000 units of penicillin (i) in saline solution, (ii) with procaine in oil and (iii) with procaine and aluminium monostearate in oil

(v) *Procaine penicillin G crystalline in sesame oil with 2% aluminium monostearate*: a free-flowing suspension of 300,000 units per ml: aluminium monostearate is the dispersing agent.

(vi) *Procaine penicillin G crystalline with potassium penicillin G crystalline in sesame oil with 2% aluminium monostearate* has 400,000 units per ml. This maintains a therapeutic level for nearly 4 days.

(vii) *Penicillin with carinamide*.—Carinamide by delaying penicillin excretion (p. 12) maintains a more prolonged high

blood level. Carinamide is given orally in 2 to 3 g. doses every 3 or 4 hours. This is suitable along with both oral and parenteral administration of penicillin.

(viii) *Penicillin with a Vaso-constrictor*.—Penicillin with adrenaline or/and ephedrine causes a more sustained effect. But this is not sufficiently popular.

COMMERCIAL PREPARATIONS.—(i) *Soluble Crystalline* sodium, potassium and calcium penicillin G in 100,000, 200,000, 500,000 and 1,000,000 i.u. ampoules. (ii) *Oil-wax suspension* in 125,000 i.u. (iii) *Procaine penicillin G* in 300,000 i.u. (for aqueous suspension). (iv) *Procaine penicillin* 300,000 i.u. with buffered crystalline penicillin 100,000 i.u. (available as pronapen, penicillin S-R and crysticillin fort.). (v) *Procaine penicillin in oil* in 300,000 i.u. (vi) *Procaine penicillin in oil* with 2% aluminium monostearate in 300,000 i.u. vials.

(1) *Gonorrhœa* is susceptible to above treatment. A single intramuscular injection of procaine penicillin 300,000 i.u. often causes remarkable improvement: may be repeated if not asymptomatic. Orally 100,000 i.u. every 3 hours (6 doses daily) for 1-2 days may also do: in resistant cases, 300,000 i.u. every 4 hours is recommended. Penicillin is of value as prophylactic after exposure and also for gonococcal complications.

(2) *Syphilis*.—The curability depends on (a) stage of the disease, (b) total dosage, (c) injection interval, (d) duration of treatment days and (e) use of chemical antisyphilitic drugs. Ambulatory treatment with procaine penicillin (or the same with aluminium monostearate) is now preferred. (i) In sero-negative primary cases, deep intramuscular injection of 600,000 i.u. each for 8 days: (ii) in sero-positive primary cases, injections for 12 days: (iii) in secondary syphilis, injections for 16 days: (iv) in first relapse, injections for 20 days: (v) in second relapse, penicillin 20 injections with arsenoxide-bismuth treatment (see p. 327). Special care is necessary for neurosyphilis and cardiovascular syphilis: more graduated doses with a preliminary chemical therapy are safer.

(3) *Bacterial endocarditis*.—S. Viridans are resistant organisms. Soluble penicillin 100,000 i.u. intramuscularly every 2 hours for 8 weeks is suitable in most cases. Procaine penicillin 400,000 to 600,000 i.u. every 12 to 24 hours may also do. Negative blood culture with dropping of temperature should happen in less than a week: if symptoms continue, a bigger dose is required. In resistant cases, treatment may have to be kept up in a little smaller dose for another 3 to 6 weeks. Streptomycin, aureomycin or chloromycetin should be tried.

(4) *Pneumonia* and *Cerebro-spinal fever* are better treated with combined sulphonamide and penicillin (the latter being given intrathecally in doses of 10,000 units once or twice daily also 300,000 to 1,200,000 units intramuscularly). Diphtheria and Tetanus are treated along with antitoxin. Wound surfaces and pus pockets are treated both locally and by parenteral administration. In severe cases with bacteriæmia, crystalline penicillin

or procaine penicillin with buffered crystalline penicillin, at least initially, is more desirable : 800,000 to 1200,000 i.u. daily.

(5) *Prophylaxis*.—Oral penicillin may be used preliminary to tonsillectomy, tooth extraction, a surgical operation or exposure to gonorrhœa. Intramuscular administration of 300,000 to 600,000 i.u. every 6 hours may be needed in severer surgical operations having a possibility of dissemination of an infection.

Toxicity.—Penicillin is remarkably non-toxic to the body tissues. Cells in tissue culture and leucocytes would tolerate concentrations hundreds of times greater than those needed for bacteriostasis and repeated injections into animals revealed no significant effect on any of the vital organs.

Thrombophlebitis near the site of injection may develop after a few days of continuous intravenous treatment, but is not often seen after intermittent injections.

Generalised *urticaria* may also occur, but the condition is usually mild. There is no evidence of increased sensitivity and treatment may be prolonged or further courses of injections may safely be given.

A *pyrogenic substance* is present in crude penicillin and though it is usually removed during purification, enough may remain to cause rigor and fever especially after intravenous administration.

Pain is common after subcutaneous or intramuscular injection. A mixture of procaine with penicillin is useful where the pain is severe.

In the systemic treatment of early localised or mild infections, a course lasting for 3 to 5 days may be sufficient. But for a general or severe local infection, treatment should continue for many days and even months.

Apparent failure of penicillin may be due to,—(1) dead tissue, such as a slough or sequestrum forming a focus of infection ; (2) an infected area not being reached by the drug ; (3) too small a dose or too infrequent application ; (4) insensitivity of the infective bacteria ; (5) loss of potency of the preparation. (Florey : British Journal of Surgery, Special Penicillin Issue, 1944).

SUMMARY.—Penicillin is active *locally* or well as by *systemic administration* against a large group of micro-organisms. Being relatively non-toxic, an enormous dose is tolerated and an infection is quickly controlled. It is used by *intramuscular injection* in *soluble* (for rapid action) and in *repository forms* (sustained action) : in a moderate infection, *orally* also.

3. Streptomycin, $C_{21}H_{39}N_7O_{12}$ (Not Official)

The next antibiotic of considerable promise is streptomycin obtained from *Streptomyces* or *Actinomyces griseus* (Waksman, 1944).

This is an *organic nitrogenous base* and contains three basic functional groups, streptidine, N-methyl glucosamine and a six-carbon nitrogen free hexose. It is soluble in water and in dilute acids. It is *more stable* in dry state and in aqueous solution than penicillin and the solution may be kept in room temperature for several days.

It is *assayed* in the same way as penicillin, but with *B. Coli* and one *unit* of streptomycin represents the activity of 1 microgram of pure streptomycin base.

Absorption and Elimination.—It is easily absorbed from intramuscular administration, distributed in the extracellular fluid and excreted in the bile and urine. It is not much absorbed from the alimentary tract and so oral administration may only be of some use locally in alimentary infection by susceptible organisms. It poorly diffuses into the cerebro-spinal fluid and so has to be given intrathecally.

ACTIVITY.—It is effective against certain *Gram-negative* and a few *Gram positive* bacteria including *acid fast organisms*.

Streptomycin is both **bacteriostatic** and **bactericidal**, probably acting by inhibiting nutrition of the pathogenic organisms.

It is especially useful in tularemia, *H. influenzae* infection and in meningitis, bacteraemia, urinary tract and pulmonary infections by *Gram-negative* organisms. It is effective in tubercular infection. Being excreted more slowly than penicillin, 1 g. and if highly purified, up to 3 g. may be given in two divided doses daily: intrathecally, up to 0.1 g. daily or on alternate days.

It is also sometimes useful in penicillin resistant staphylococcic, streptococcic, pneumococcic, gonococcic, and meningococcic infections.

About 40 to 80% of streptomycin is excreted in the urine suggesting the reason for its being useful in urinary tract infections.

TOXICITY.—Unlike penicillin, streptomycin has (a) *histamine effect* (flushing, headache and rapid fall in blood pressure): this is probably due to impurities. (b) *Allergic reactions* (itching, maculo-papular eruptions, a rise in temperature, nausea and vomiting). (c) *Neurological effects* causing vestibular disfunction and deafness. These develop in 3 weeks. (d) *Renal irritation* causing cylindruria and diminution of renal efficiency.

By catalytic hydrogenation, probably at the carbonyl group, *dihydrostreptomycin* is produced which has the action of streptomycin but is less toxic and can be given in a slightly bigger dose. This is available as sulphate or hydrochloride: it is ineffective against tubercle bacilli made resistant to streptomycin.

Recently from another strain of streptomycetes, *neomycin* has been prepared and this does not usually make resistant tubercle bacilli and promises to be an advance.

CLINICAL APPLICATION.—Streptomycin is especially useful in (i) *tubercular infections*: (a) In meningitis, the drug is given intramuscularly and intrathecally for about 3 months with moderate success. (b) In miliary tuberculosis, the results are better. (c) In pulmonary infection in the exudative phase, it is of great value: 1 g. daily in two 0.5 g. doses, has to be continued fairly long: improvement is most marked in the first 3 months and the treatment must be accompanied by collapse therapy or/and P.A.S. (d) In tracheo-bronchial and laryngeal

infection: tuberculosis of bones, cartilages, lymph nodes, intestinal canal and tubercular sinuses: in these 1 to 2 g. daily for 2 to 4 weeks may do.

(ii) In *Gram-negative, bacterial infections* (see p. 172) often streptomycin is more effective. As a shorter course is usually needed, a daily dose of 3 g. may be tolerated. In many of these Chloromycetin and Aureomycin are also effective.

(iii) In *Gram-positive bacterial infection* and in *gonorrhœa*, penicillin is more effective: streptomycin may be used in resistant cases.

(iv) In *tularæmia*, streptomycin is effective but aureomycin is probably better.

(v) In *plague* and sometimes in *actinomycosis*, streptomycin may succeed.

(vi) In *meningitis* due to *H. influenzae* (aureomycin is also useful), *B. Coli*, *Ps. pyocyanea*, *proteus* and *staphylococcus pyogenes* infection streptomycin is useful, may be combined with sulphonamides. *Septicæmia* by these organisms is also amenable to streptomycin.

(vii) In *urinary tract infection* due to *B. Coli*, *Proteus*, *Ps. pyocyanea*, *Str. faecalis* and *Staphyl. pyogenes*, streptomycin often succeeds.

(viii) A *local sepsis* by the above organisms may be treated with streptomycin.

It must be remembered that some of the organisms become drug-fast and escape destruction: these may cause severe relapse on which streptomycin is no longer effective.

COMMERCIAL PREPARATIONS.—*Streptomycin Sulphate* dry 1, 2 and 5 g. vials also 25 c.c. vials containing 0.5 g. and 1 g. of streptomycin base. *Dihydrostreptomycin Sulphate* in 1 and 5 g. vials. *Combiotic* has procaine penicillin 300,000 units, sodium penicillin 100,000 units and dihydrostreptomycin 1 g.

4. Chloromycetin, Chloramphenicol (Not official)

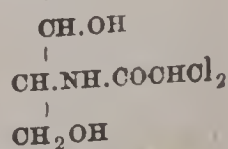
This crystalline antibiotic originally obtained from *streptomyces venezuelæ* is now synthesised.

It is available in 250 mg. sealed kapseals and administered orally. Being intensely bitter, it has to be given to infants as powder mixed with honey or a punctured capsule is used as suppository.

It is rapidly absorbed and an effective blood level is obtained in half to one hour. About 10% of it is excreted in the urine unchanged.

TOXICITY.—It is well tolerated but occasionally, headache, nausea, vomiting, diarrhœa and skin eruptions may appear: rarely vasomotor failure: if continued long, leukopenia.

CLINICAL APPLICATION.—Chloromycetin is very effective in infection by the enteric group, rickettsia, salmo-



mella and dysentery : also useful in ulcerative colitis, brucellosis, many urinary tract infections (both bacillary and coccal), pertussis, bacterial pneumonia, primary atypical pneumonia, lymphogranuloma venereum and infectious mononucleosis also probably in gonorrhœa and syphilis : psittacosis, mumps, trachoma, chicken-pox and herpes zoster may have some response.

DOSE.—In most cases 50 mg./kg. body weight daily in 4 to 6 divided doses for several days : children require proportionally slightly bigger dose. As the condition improves, the dose is reduced and is continued up to convalescence in even smaller doses.

A CONVENIENT DOSE SCHEDULE for an adult of about 130 lbs. body weight : (i) for *typhoid*, *typhus* and *brucellosis* : 2 (sometimes 3) capsules every four hours till afebrile and every six hours afterwards for a total period of 10 to 12 days. (ii) *Primary atypical pneumonia* : 2 capsules every 4 hours till 12 and then every 8 hours for 5 days. (iii) *Ulcerative colitis* : 2 capsules every 4 hours till much improved. (iv) *Urinary tract infection* : 8 to 12 capsules daily in 4 divided doses till the urine is clear and next one capsule 3 to 4 times daily for 4 to 7 days. (v) *Pertussis* in children below one year, one capsule initially and $\frac{1}{2}$ capsule 6 hourly for 4 to 7 days. (vi) *Lymphogranuloma venereum*, *granuloma inguinale* : 4 capsules every 6 to 8 hours for 10 to 14 days. In all acute conditions, coramine 15 min. every 4 hours orally should better be given. (vii) *Other infections* may need 8 to 12 capsules daily for 7 days.

5. Aureomycin (Not official)

This antibiotic is obtained from *S. aureofaciens* with a faint golden-yellow colour (hence named *aureomycin*). It is soluble in acid and alkaline medium : but in alkaline solution, it rapidly loses its activity.

ACTION.—Its specific action is obvious against certain organisms, both Gram positive and Gram-negative (resistant staphylococci and many urinary tract infections) also salmonella infections : the rickettsias, tularemia and atypical pneumonia : viruses of psittacosis, herpes and lymphogranuloma venereum : it is also useful against spirochaetes as of relapsing fever, leptospirosis and primary syphilis : in amoebiasis, favourable reports are forth coming.

Aureomycin is easily absorbed from oral administration and rapidly appears in the urine, about 10 to 15% of the dose being excreted in the urine. *Daily dose* in most cases is 25 to 50 mg./kg. body weight given in capsules of 250 mg. each divided into 4 doses one six hourly.

Signs of intolerance are nausea, vomiting and diarrhœa.

Comparing chloromycetin and aureomycin, it may be said that (i) both are effective in rickettsia infections : (ii) in lymphogranuloma group, both are effective and aureomycin is better : (iii) in typhoid fever chloromycetin only is effective : (iv) in

primary atypical pneumonia, aureomycin is preferred : (v) in brucellosis, tularæmia and psittacosis, aureomycin is more useful : (vi) a urinary tract infection (except by *B. proteus*) especially by organisms refractory to sulphonamides, penicillin and streptomycin is often controlled by aureomycin : (vii) in syphilis and in other spirochætal infections, aureomycin is proving its worth : (viii) aureomycin borate in $\frac{1}{2}\%$ solution has a wide range of therapeutic activity in ocular infections.

AVAILABLE as 250 mg. capsules : spersoid powder, ophthalmic drops and ointments and troches.

6. Terramycin (Not official)

This is of more recent introduction and has been found useful in (a) *upper respiratory tract* infection (pharyngitis, tonsillitis, laryngotracheitis and pertussis) : (b) *acute pulmonary infections* as pneumonia and lung abscess and (c) *urinary tract infections* and (d) *rickettsial, brucella and salmonella* infections.

DOSE, 0.5 g. every six hours (2 g. daily) orally may be sufficient. *Locally*, the ointment is applied on the skin in many pyogenic infections.

AVAILABLE as capsules, elixir, intravenous ampoules, ointment and troches.

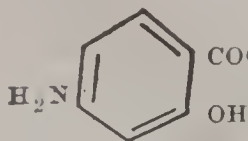
TYROTHRICIN, prepared from soil bacillus (*B. brevis*) is used in isotonic solution containing 0.5 mg. of it per c.c. for local application by instillation, irrigation or wet dressing into nasal sinuses, urinary bladder and pleural cavity. *Tyrozites* throat lozenges are used.

PROTHRICIN, contains Tyrothricin 0.02% and propadrine 1.5% for nasal instillation.

7. Para-aminosalicylic Acid (P.A.S.), Not official

Berheim (1940) discovered that salicylic and benzoic acids stimulate the metabolism of tubercle bacilli. Lehmann found that para-aminosalicylic acid has the opposite effect (strong tuberculostatic). Many cases of tubercular infection have since been treated with it with much success.

Para-aminosalicylic Acid is a crystalline powder, sparingly soluble in water : the sodium salt is easily soluble. It is more stable in neutral or slightly alkaline solution but is decomposed in acid medium.



P.A.S. is readily absorbed from the intestine and is excreted in the urine (about half of the excreted amount is in acetylated form). A single oral dose of 2 to 4 g. causes the maximum blood level in 2 to 5 hours and in 3 to 6 hours, urinary excretion is nearly complete and so several 4 hourly doses are necessary, the total dose in 24 hours being in most cases 14 g. (this causes an adequate bacteriostatic blood level). Given in bigger doses, symptoms of gastro-intestinal and renal irritation may appear :

these are mitigated by giving the sodium salt (in a slightly bigger dose than P.A.S.). P.A.S. treatment may be combined with sulphaa., penicillin and streptomycin. The bacteria do not become drug-fast.

The drug is available in enteric coated granules, powder, pills, tablets and in dragees.

CLINICAL APPLICATION.—(a) *Pulmonary tuberculosis* especially in the exudative stage (where the drug can diffuse well), a daily dose of 14 g. (may be increased to 18 g.) is given for 3 to 6 months : the patient should be afebrile for 3 to 4 weeks before the treatment is concluded. An all round clinical and radiological improvement takes place. (b) *Laryngeal* and *tracheo-bronchial tuberculosis* is treated in the same way. (c) In *intestinal tuberculosis*, a lower dose as 8 g. daily is administered and if well tolerated, increased to 12 g. daily. (d) In urogenital tuberculosis, initially 8 g. and increased to 14 g. daily for 3 months is necessary. (e) In *meningeal* and *miliary tuberculosis* 18 g. daily with 1 to 2 night doses and if no improvement, Na-P.A.S. in 25 to 30 g. daily should be given. In this and in most other severer cases, streptomycin 1 to 2 g. intramuscularly daily is also essential. (f) In *tubercular empyema*, *extra pleural cavities* also in a *joint*, the pus is evacuated by aspiration and 25 to 300 c.c. of 5 to 10% Na. P.A.S. solution is introduced twice weekly for 2 weeks and afterwards once weekly.

The doses for children are proportionately less. The drug is administered during or after food.

SUMMARY.—The practical applications of *sulphonamides* and *antibiotics* in order of preference :

- (1) *Anthrax*.—Sulphonamides and penicillin.
- (2) *Brucellosis*.—Aureomycin, chloromycetin and streptomycin.
- (3) *Chancroid*.—Aureomycin, streptomycin and sulphonamides.
- (4) *Diphtheria*.—With antitoxin, sulphonamides and penicillin.
- (5) *Dysentery*.—(a) *Amæbic*.—Sulphonamide-penicillin (axiliary to chemical amæbicides) and aureomycin. (b) *Bacillary*, sulphonamides, aureomycin and chloromycetin.
- (6) *E. Coli*.—Sulphonamides, streptomycin, aureomycin and chloromycetin.
- (7) *Gas-gangrene*.—Penicillin and sulphonamides.
- (8) *Gonococci*.—Penicillin, sulphonamides, streptomycin and chloromycetin.
- (9) *H. Influenzæ*.—Streptomycin, chloromycetin and aureomycin.
- (10) *Lymphogranuloma venereum* and *Granuloma inguinale*.—Aureomycin and chloromycetin.
- (11) *Meningococcal infection*.—Sulphonamides and penicillin.
- (12) *Pertussis*.—Chloromycetin and aureomycin.
- (13) *Plague*.—Streptomycin and sulphonamides.
- (14) *Pneumococcal infection*.—Sulphonamides, penicillin, aureomycin and chloromycetin.
- (15) *Pneumobacillary infection*.—Streptomycin, aureomycin and chloromycetin.
- (16) *Psittacosis*.—Aureomycin and chloromycetin.
- (17) *Rickettsial infection*.—Aureomycin and chloromycetin.
- (18) *Salmonella infection* (Food poisoning).—Chloromycetin, aureomycin and sulphonamides.

- (19) *Staphylococcic infection*.—Penicillin and sulphonamides.
- (20) *Strepto. haemolyticus infection*.—Penicillin and sulphonamides.
- (21) *Strepto. viridans* (bacterial endocarditis) *infection*.—Penicillin : in resistant cases, streptomycin and aureomycin.
- (22) *Spirochaetosis* and *Leptospirosis*.—Penicillin and aureomycin.
- (23) *Tetanus*.—With antitoxin, penicillin.
- (24) *Tuberculosis*.—Streptomycin with P.A.S.
- (25) *Tularaemia*.—Aureomycin.
- (26) *Typhoid group of Fevers*.—Chloromycetin.
- (27) *Urinary tract infection*.—Sulphonamides, penicillin, streptomycin, aureomycin and chloromycetin (depending on the nature of the bacteria concerned).
- (28) *Vincent's infection*.—Penicillin.
- (29) *Virus infection*.—(a) Atypical pneumonia : chloromycetin and aureomycin : (b) Herpes zoster, infectious mononucleosis, measles, mumps, varicella and variola.—Chloromycetin may be useful.

VII. Chemotherapy of Leprosy

So long *hydnocarpus* oil was the only remedy for the treatment of leprosy giving some relief but *synthetic sulphones* are now proving to be of greater value.

1. OLEUM HYDNOCARPI (*Ol. Hydnocarp.*), *Tubrak taila*.

This is a fatty oil expressed cold from the fresh ripe seeds of *Hydnocarpus Wightiana* : yellowish or brownish yellow in colour with a characteristic smell and acid taste. The active principle is *Hydnocarpic Acid*. Obtained from Southern India. This is in IND. PHARM. LIST also.

The oil consists chiefly of glycerides of unsaturated fatty acids with a closed 5 chain carbon ring. Should be kept protected from light in a cool place. DOSE, 5 to 15 minims increasing to 60 minims or 0.3 to 1 ml. increasing to 4 ml.

OFFICIAL PREPARATIONS.—(i) *Oleum Hydnicarpi Aethylicum* (*Ol. Hydnicarp. Aeth.*), Ethyl esters of hydnicarpus oil. This is a colourless or faintly yellow transparent oil, with a characteristic odour and slightly acid taste : prepared by esterifying the fatty acids of hydnicarpus oil, with ethyl alcohol or with industrial methylated spirit and subsequent purification. DOSE, as of the oil of Hydnicarpus. (ii) *Injectio Olei Hydnicarpi* (*Inj. Ol. Hydnicarp.*), See p. 45. Stored in a cool place protected from light. (iii) *Injectio Olei Hydnicarpi Aethylici* (*Inj. Ol. Hydnicarp. Aeth.*), See p. 45. DOSE, 30 minims increased to 75 minims or 2 to 5 ml. intramuscularly or subcutaneously.

Non-official Preparations

OLEUM CHAULMOOGRE, Gynocardia oil, is the fatty oil expressed from the seeds of *Hydnocarpus Kurzii* : contains unsaturated fatty acids consisting of 5 chain carbon ring and twelve CH₂ groups in the side chain. Hydnicarpic acid has only ten CH₂ groups. The tree grows in the forests of Sikkim, Chittagong, Sylhet, Upper Burma and the Malaya Peninsula. Oil should be kept in a well-closed container in a cool place protected from light. This is in IND. PHARM. LIST.

DOSE, as of the oil of Hydnicarpus.

MOOGROL, Ethyl chaulmoograte, is given intramuscularly in 1 to 6 c.c. doses, slowly increased or $\frac{1}{2}$ to 2 c.c. intravenously twice a week.

SODIUM HYDNOCARPATE, ALEPOL, the lower melting fraction of sodium salts of Hydnicarpus Acids in 3% solution, is given subcutaneously, intramuscularly or intravenously, in increasing doses.

Pharmacology [and Therapeutics]

Hydnocarpus and Chaulmoogra oils are time-honoured remedies of Ayurveda for the treatment of leprosy, but are now yielding place to synthetic sulphone compounds.

EXTERNALLY.—Rubbed into the intact skin, these oils are rubefacient but cause greater irritation on a raw surface.

TAKEN INTERNALLY, these are gastro-intestinal irritant especially in big doses.

SPECIFIC ACTION.—Either rubbing in the oil into the leprotic area or taking this orally is now obsolete.

Injection method is current, starting with a small dose and slowly increasing. Chaulmoogra or Hydnocarpus oil, or the ethyl esters of the oils were given intramuscularly with creosote, camphor (one of each) and olive oil 2·5 (called 'E.C.C.O.'): starting with 0·25 c.c. But as these caused pain, a water soluble preparation, sodium hydnocarpate in 3% solution was given intravenously twice a week starting with 0·5 c.c. or more. This often caused reactions, local and constitutional, also phlebitis and blocking of the veins and are now out of use.

Now, hydnocarpus oil itself prepared from ripe fresh seeds with 4% of creosote is infiltrated intradermally directly into the affected area ("plancha" method). The maximum dose is 5 c.c. Not more than one drop should be introduced by each puncture, 60 to 80 such punctures being made all over the area.

This has been found to be effective and, in addition, less painful and cheaper. The treatment has to be continued for about 6 months.

All these are available in bulk or in 2 c.c. ampoules for injection.

MODE OF ACTION is uncertain, may be some special selective action on the acid-fast organisms.

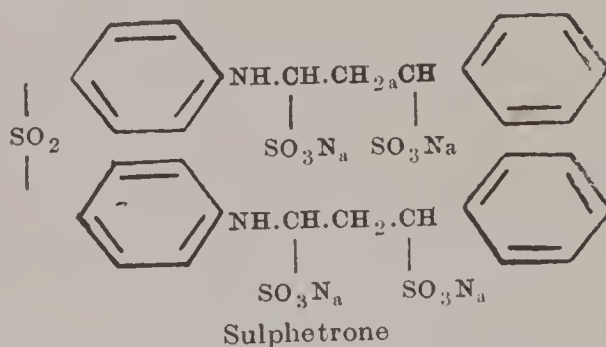
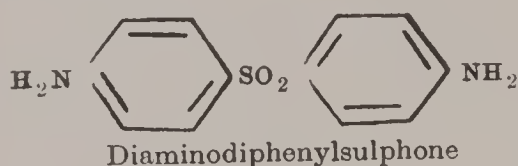
TOXIC SYMPTOMS sometimes follow, more commonly after injections of chaulmoogra derivatives. These are pain and induration at the site of the injection and occasionally headache, malaise, dizziness, fever, insomnia, local and abdominal pain and a general sensation of heat; pain in the chest, sensation of suffocation and cough: also albuminuria. (Wade, Lara and Nicolas, 1924).

2. SULPHONE DRUGS IN LEPROSY (Not official).

The sulphone drugs recently introduced in practice, commenced with 4·4'-diamino-diphenylsulphone (commercial names are *Avlosulphone* and *Diphone*) and followed by other allied compounds with the commercial names of *Promin*, *Diasone*, *Sulphetrone* (and *Novotrone*) and *Promizole*. These were originally tried in tuberculosis but did not succeed.

THE MODE OF ACTION AND DOSE.—The sulphone drugs cause clinical improvement in *lepromatous leprosy* probably by certain bacteriostatic or bacteriocidal action. A prolonged treatment spreading over a year or more is necessary, even: then some bacilli may escape destruction.

The parent sulphone *diamino-diphenyl-sulphone* (D.D.S.) is the most toxic of all but with an initial oral dose of 0.1 g. may be tolerated which is gradually increased to 0.3 g. or more daily. *Promin* is not tolerated orally and in 2 to 5 g. (5 to 12.5 c.c. of promin solution) doses may be given intravenously for 6 days in a week : this causes quick blood concentration but the elimination is rapid and so this is suitable for an acute emergency like a threatened blocking of the larynx from lepromatous involvement but has to be followed up by drugs of more sustained action.



Both *diasone* and *sulphetrone* are well tolerated by the mouth but *diasone* is more readily absorbed than *sulphetrone*. *Sulphetrone* is however least toxic of all and is more suitable for prolonged administration. *Sulphetrone* may also be given intramuscularly. *Diasone* is started orally with one tablet ($\frac{1}{3}$ g.) and gradually increased to 6 tablets (2 g.) daily but in most patients, more than 4 tablets are not tolerated. *Sulphetrone* is started with one tablet (0.5 g.) 3 times daily (1.5 g.) and gradually increased to 12 tablets (6 g.) daily for 6 days in the week. Intramuscularly, 1 to 5 c.c. of 50% solution (available in ampoules) or is to be given twice a week : a blood level of 5 mg.% is to be maintained. The administration should be continued for 6 months to 2 years : often the improvement is obvious in all stages of lepromatous leprosy.

Intolerance.—The toxic symptoms are progressive anæmia, gastro-intestinal irritation, burning sensations in the hands and feet, muscular weakness and palpitation : drug rash and fever may occasionally appear.

So before commencing the treatment, a blood count should be made and the hæmoglobin must be at least 75%. If this is much less, a preliminary treatment with iron and vitamin B complex must be given and during the whole course of treatment, the blood should be periodically examined : if necessary, the treatment should be suspended for short periods.

SUMMARY.—Lepromatous leprosy may be controlled by oil of *hydno-capus* injection but more surely by *sulphone* compounds orally or parenterally: treatment is to be continued for 6 months to 2 years. Toxic symptoms are to be guarded against.

VIII. GLANDS OF INTERNAL SECRETION USED THERAPEUTICALLY

The Suprarenals, Pituitary body, Thyroid gland, Parathyroid glands, Deodenum, Pancreas, Stomach and the Liver have powerful internal secretions (hormones) which are necessary for the normal bodily functions. When for some disease, the normal secretion is deficient, the extract of any of these glands from a big animal as an ox, a pig or a sheep, has been used therapeutically with benefit. Recently, several of these hormones have been prepared synthetically.

Of other glands of internal secretions, gonads are also therapeutically active especially the highly potent synthetic preparations but the actions of Thymus, Spleen, Pineal glands and other glands of minor importance are less certain.

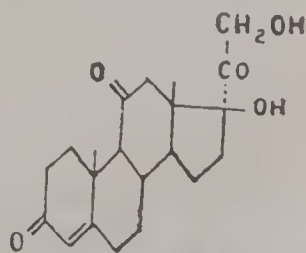
The Suprarenals have two portions.—the *cortex* and the *medulla*. The internal secretion of the former is so essential for life that its absence rather than that of medulla in an adrenalectomised animal invariably causes death. This however, may be prevented by therapeutic administration of the cortical extract.

Phenomena of deficiency are also seen with the pituitary (more of the anterior portion), thyroid and parathyroid glands, pancreas, stomach and liver. Their therapeutic administration resulting in cure is of the nature of replacement therapy. The suprarenal medulla secreting adrenaline acts through activation of the sympathetic nervous system and this action is not so definitely the replacement of a deficiency: so this will be considered in connection with drugs acting on the sympathetic nervous system.

SUPRARENAL CORTEX

The hormones of the suprarenal cortex are (i) *Carbohydrate metabolism hormones*: 17-hydroxycorticosterone and 11-dehydro 17-hydroxycorticosterone (*cortisone* or compound E). (ii) *Electrolytic and water-metabolism hormone*: desoxycorticosterone (maintains sodium balance) and 17-hydroxy corticosterone (maintains sugar level in the blood and glycogen in liver). (iii) *Sex hormones*: suprarenal cortex is also the source of androgen, œstrone and progesterone (in addition to their production by the gonads).

Cortisone or compound E has now drawn much attention for its marvellous effect of causing considerable improvemant



Cortisone

(clinical, pathological and hæmatological) in rheumatoid arthritis. The Anterior Pituitary Adrenocorticotrophic hormone (A.C.T.H.) has also similar effects: it is also useful in rheumatic fever, disseminated lupus erythematosus and gouty arthritis. The cost of their production from natural sources is prohibitive for general use. Dose for rheumatoid arthritis is 100 mg. daily intramuscularly for several weeks and for other conditions a higher dose.

DEOXYCORTONI ACETAS (*Deoxycort. Acet.*), desoxycortico-sterone acetate, $C_{23}H_{32}O_4$ is 21-acetoxy- Δ^4 -pregnene-3:20-dione, prepared by the action of glacial acetic acid on 21-diazo- Δ^4 -pregnene-3:20-dione, obtainable from degradative oxidation product of stigmasterol or cholesterol.

Colourless crystals or crystalline powder, inodorous and insoluble in water, soluble in alcohol (95%), acetone, propylene glycol and in fixed oils.

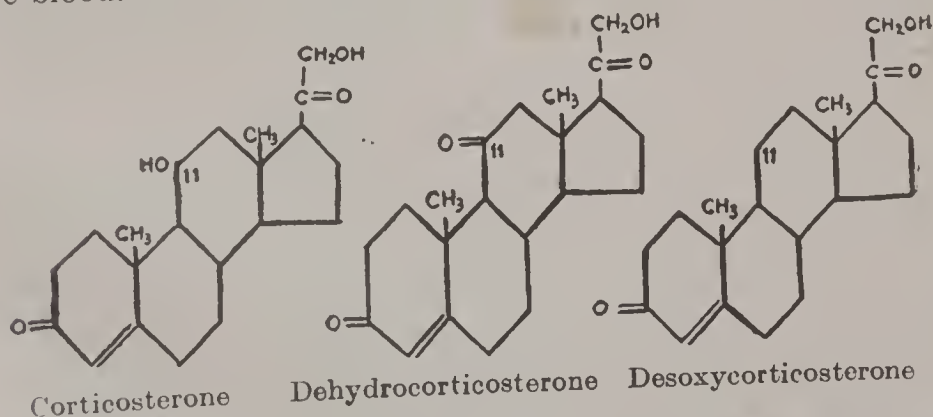
Dose, 1/30 to 1/6 grain or 2 to 10 mg., intramuscularly: 3 to 6 grains or 0.2 to 0.4 gramme by implantation.

Injectio Deoxycortoni Acetatis (*Inj. Deoxycort. Acet.*), See p. 43. Dose as of the above.

When the strength is not stated, a solution containing 5 mg. in 1 ml. or 1/12 gr. in 15 min. shall be dispensed.

Pharmacology [and Therapeutics]

The surgical removal of the *suprarenal cortex* is followed by muscular asthenia, gastro-intestinal disturbances, diminished metabolism with loss of weight, lowering of body temperature, and susceptibility to exposure to heat and cold, lowered blood pressure and fluid volume, hypoglycæmia and increase in blood phosphate and non-protein nitrogen. In addition there is marked lowering of muscle and liver glycogen and also of sodium chloride and bicarbonate and increase of potassium in the blood.



The cortex is also related to the anterior pituitary, the latter producing adreno-corticotrophic hormone. Cortical new-growth in children causes premature bodily development and in a woman, manly character.

The chemical structure of the active principle of adrenal cortex has close resemblance to the same of the sex hormones.

especially to testosterone. Though the different principles have divergent actions, like sex hormones, by esterification the intensity and duration of these actions are increased.

The *symptoms* of cortical deficiency are complex. It has been postulated that these are mainly due to failure in maintaining the adequate blood volume, loss of capillary tone and circulatory stagnation: the rest follow as a consequence (Swingle). Others believe that hypoglycæmia and marked deficiency of liver and muscle glycogen are the main factors (Britton). Others again think that there is a general metabolic disturbance being related to gonadal dysfunction (Hartman).

Disturbed sodium chloride metabolism is obvious in an adrenalectomised animal. Sodium chloride and bicarbonate of blood plasma are lowered causing dehydration, diminished blood volume and lowered circulatory flow, a condition resembling shock. In Addison's disease (degenerative disease of the cortex) also, sodium chloride is lowered in the plasma and increased in the urine.

In spite of these points of partial resemblance, it is obvious that something more is missing in cortical deficiency diseases to explain the causes of other symptoms. Probably the complex hormone is essential for some very basic reaction in the organism without which many physiological functions are deranged.

Administration of cortical hormone extract to an adrenalectomised animal, maintains normal glucose and sodium chloride level in the blood and weakness and quick tiredness of the limbs disappear in a few days. The gland extract even in moderate over dose is nontoxic but not desoxycorticosterone: this given in overdose causes retention of sodium chloride with increase in extracellular fluid.

Clinical conditions showing cortical deficiency are Addison's Disease, surgical shock, severe burns, acute intestinal obstruction, acute infective fevers (as typhoid, cerebrospinal fever and toxic diphtheria), hyperemesis gravidarum, pituitary cachexia, infantile marasmus and chronic fatigue.

[In (i) severe pathological cortical deficiency, standardised cortical extract (*cortin*) 25 c.c. is given intramuscularly and in a crisis, a big dose as 50 to 100 c.c. is given intravenously and desoxycorticosterone 20 mg. intramuscularly. In addition, sodium chloride 10 g. with sodium bicarbonate 5 g. orally daily and/or sodium chloride and glucose solution intravenously ensuring liberal supply of fluid also. (ii) In many chronic cases, 6 to 8 g. of sodium chloride orally and 2 to 5 mg. desoxycorticosterone acetate intramuscularly once daily many give clinical relief. During this treatment, if the body weight is increased by more than 0.3 kg. daily (indicating tissue œdema), the treatment is suspended. Desoxycorticosterone may also be given orally and sublingually and in a suitable case by subcutaneous implantation (100 mg.). The signs of improvement are increased

appetite and disappearance of vomiting : increase of muscular efficiency, diminution of pigmentation and gain in body weight : blood pressure tends to go up and the body temperature becomes normal.

Although desoxycorticosterone is mainly concerned with electrolytic metabolism, it is capable of prolonging life in cortical deficiency diseases. Being more easily available, this has largely replaced the natural cortical extract therapy except during crisis.

SUMMARY.—Originally the active extract of the suprarenal cortex was obtained from the adrenal glands of large animals and called *cortin*. Desoxycortico-sterone (*Doca*) has been recently synthesised having the main actions of cortin but cortin itself has a more comprehensive action which is manifested more quickly. So in an acute crisis cortin should be used followed by deoxycortone and in a chronic case, deoxycortone may be sufficient.

ESCHATIN, **CORTIN** and **EUCORTONE** (Cortical extract) in 10 c.c. vials : **PERCORTAN** (Desoxycorticosterone acetate) and **CORTIRON** in oily solution 4 to 20 mg. daily, intramuscularly are administered. *Doca* (Desoxycortico-sterone acetate) dissolved in arachis oil, in 5 c.c. rubber capped vials, each c.c. containing 2, 5 mg. and 10 mg. of the crystalline substance.

PITUITARY EXTRACT

ANTERIOR LOBE OF PITUITARY BODY

It has recently been possible to fractionate the different active principles of the anterior pituitary. These are (i) *Growth hormone* : this in a hypophysectomized animal can maintain normal growth. (ii) *Gonadotropic hormones* : (a) follicle stimulating on the ovaries and spermatogenic on the testes : (b) luteinizing, stimulating interstitial cells of the ovaries and testes (corpus lutea formation and increased activity of Leydig cells of the testes). (iii) *Thyrotrophic hormone*, stimulating thyroid activities. (iv) *Adrenotrophic hormone* stimulating the adrenal cortex : Recently this (A.C.T.H.) has attracted much attention. (v) *Lactogenic hormone* : this has been obtained in crystalline form : this can stimulate lactation also bodily growth and the gonads. (vi) *Pancreatrophic hormone* : increases insulin production and (vii) *Diabetogenic hormone* : either suppresses carbohydrate oxygenation or increases carbohydrate formation.

It is sometimes prescribed in various ways especially for its action on the sex glands. In the male, this hormone determines spermatogenesis and secretion of the male sex hormone by the testes. In the female, it acts through two hormones, both acting on the ovary. The one, *Prolan A*, produces *oestrin*. This induces menstruation and grows enormously during pregnancy and finally activates oxytocin to start labour. The other, *Prolan B* produces *lutein* which favours the implantation of the ovum. Further, it is responsible for the development of the placenta, it stops menstruation and maintains pregnancy by relaxing the uterus and inhibiting *oestrin* and it also causes development

of the breasts and lactation. Prolans are eliminated by the kidneys all throughout pregnancy, the maximum being reached in the 4th or the 5th month. Their presence in the urine is a reliable diagnostic test for pregnancy (*Aschheim-Zondek Test*). The pregnancy is terminated by diminution of luteal hormone, increase of œstrin and activation of oxytocin in the posterior lobe of the pituitary gland.

Recently considerable therapeutic possibilities of **sex hormones** have developed in case of deficiency, mainly in the females and to some extent in the males also.

THE SEX HORMONAL AGENTS

These have been divided into two groups : (i) *Gonadotropins* : these stimulate the gonads to secrete their respective hormones and (ii) *sex hormones*, the natural secretions of the gonads.

I. Gonadotropins are of 2 kinds : (a) those obtained from the anterior pituitary or (b) elaborated by the chorionic tissue of pregnancy.

Anterior Pituitary hormone activates the ovaries to their œstrogenic and luteinizing activities. This hormone has as yet not been obtained from the gland for therapeutic use in any large quantity. The commercial product having similar action is obtained from (i) *human pregnancy urine* and (ii) from the *serum of pregnant mares* : the source of these two is the chorionic tissues of the placenta. Most of the preparations contain both the hormones, some more of one than of the other. Their important clinical applications are in the treatment of delayed onset of puberty and of cryptorchidism.

1. GONADOTROPHINUM CHORIONICUM (*Gonadotr. Chorion.*).

Chronic gonadotrophin is the gonad-stimulating substance obtained from the *urine* of pregnant women : prepared by its precipitation with concentrated alcohol, drying in vacuo and adjusting if necessary by adding sterile lactose upto the potency of the standard preparation. A white or fawn powder, soluble in water. The *unit* is the specific activity of 0.1 mg. of the standard preparation.

Dose, 100 to 500 units by intramuscular injection.

Injectio Gonadotrophini Chorionici (*Inj. Gonadotr. Chorion.*), See p. 43.

2. GONADOTROPHINUM SERICUM (*Gonadotr. Seric.*).

Serum gonadotrophin is the follicle-stimulating substance obtained from the *serum* of pregnant mares between 60th to 75th days of pregnancy : prepared by its precipitation with concentrated alcohol, drying in vacuo and adjusting if necessary by adding sterile lactose upto the potency of the standard preparation. A white powder, soluble in water.

Dose, 200 to 1000 units by intramuscular injection.

Injectio Gonadotrophini Serici (*Inj. Gonadotr. Seric.*), See p. 43.

The commercial preparations as *Antuitrin S*, *Pregnyl*, *Prolan*, *Physer* and *Gonan* have been obtained from pregnancy urine and placenta and are mainly luteinizing. *Antostab*, *Antex*, *Gestyl* and *Serogan* prepared from pregnant mare's serum are follicle-

stimulating or spermatogenic. These are standardized biologically in rat units and have not been prepared in crystalline form. These are available in ampoules and administered intramuscularly.

These are effective *provided the gonads can be made to functionate* by stimulation and in a certain number of cases, the benefit is permanent.

(i) CHORIONIC GONADOTROPIN is used (a) in the *female* for functional menorrhagia in 100 to 500 units doses daily or every other day : 100 units for habitual abortion biweekly in the first 6th to 8th months of pregnancy and in threatened abortion, 200 units or more daily. (b) In the *male*, it causes increased production of testosterone causing growth of the secondary sex organs and favouring descent of the testes (correcting cryptorchidism) : dose is 200 to 500 units 2 to 5 times weekly for 6 to 8 weeks. For acne vulgaris of the adolescents, 200 units are given on alternate days.

(ii) SERUM GONADOTROPHIN is used (a) in the *female* to supplement oestrogens in delayed puberty, sterility from anovular menstruation and in hypomenorrhœa.

Primary amenorrhœa with maldevelopment : 400 units daily for about 12 weeks or 1000 units every 7th days, till menses appeared. In *anovulatory sterility*, 400 units daily for 3 days in the second half of the cycle. For *lactational amenorrhœa*, this dose is given in the first half of the probable normal cycle calculated retrospectively.

(b) In the *male*, it is given with tocopherol acetate to increase spermatogenesis.

Delayed puberty (with testes in the scrotum) in the male, 200 to 300 units daily or 400 units on alternate days till changes appear. *Deficient spermatogenesis* of endocrinal origin : 400 units daily for 3 weeks (increased if necessary to 1000 units daily for 48 days).

SUMMARY.—*Chronic Gonadotropin* is used for luteining effects in the female and for descent of the testes in the male ; *Serum Gonadotrophin* is oestrogenic in the female and spermatogenic in the male.

OTHER COMMERCIAL PRODUCTS.—*Antuitrin S* (chorionic gonadotrophin each has 1000 units). *Pituitary Gonadotrophin* (Prolactin) in 1000 units vial. DOSE, 1 c.c. *Luteotrophin* (Prolactin) in 1000 units vial. DOSE, 1 c.c. *Synapoidin* (combined anterior pituitary and chorionic gonadotrophin) in 5 c.c. vial. DOSE, $\frac{1}{2}$ to 1 c.c. for hypogonadism as amenorrhœa, sterility, functional uterine bleeding, cryptorchidism and Frohlich's syndrome.

Cortrophin (Adrenocorticotrophic hormone of Ant. Pituitary) in 5 units and 10 units ampoules.

II. The Sex hormones.—The actual hormones are directly obtained from the ovaries or testes or prepared synthetically. These in the *female* are either follicular (œstrone, $C_{18}H_{22}O_2$) or luteal (progesterone, $C_{21}H_{30}O_2$) hormone. Both chemically are sterols and Doisy also Butenandt (1929) first isolated one in crystalline form from pregnancy urine and called œstrone. This

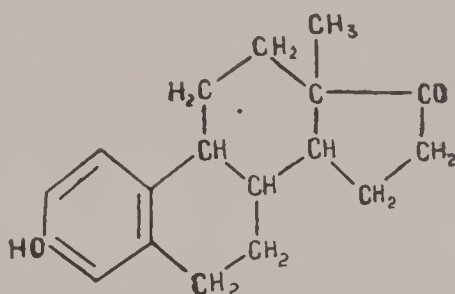
by hydrogenation produced a substance *œstradiol*, five times more active; these are administered intramuscularly. Progesterone was isolated from corpus luteum in 1934. Synthetic œstrogenic substance *stilbœstrol*, 2 to 4 times more active than œstrone is capable of oral administration also. Esterification of the follicular hormone with benzoate or propionate, œstradiol benzoate or stilbœstrol dipropionate is slowly absorbed from intramuscular injection and has a considerably prolonged biological effect. Progesterone has also been synthetised. The dose is measured by units; of œstradiol benzoate 0.1 microgram and progesterone 1 mg. of the standard are taken as one international unit.

The male hormones are *androsterone*, $C_{19}H_{30}O_2$ (from male urine) and *testosterone*, $C_{19}H_{28}O_2$ (from testicular tissue).

A. Female Sex Hormones

1. **ŒSTRONUM** (*Oestron.*), Ketohydroxyœstrin, Folliculin, Theelin. $C_{18}H_{22}O_2$: 3-hydroxy-17-Keto- $\Delta^{1.3.5}$ -œstratriene.

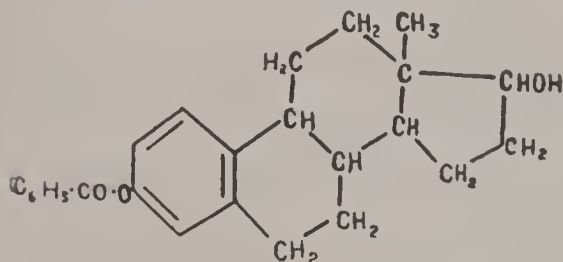
May be prepared from the urine of certain mammals. Inodorous, colourless crystals, very sparingly soluble in water; slightly soluble in concentrated alcohols and solvent ether. Soluble in chloroform, acetone, benzene and in fixed oil, also in aqueous solution of alkali hydroxides. Dose, Orally 1/60 to 1/6 grain (10,000 to 100,000 units) or 1 to 10 mg.



Tabellæ Œstroni (*Tab. Œstron.*), See p. 57.

COMMERCIAL PREPARATIONS are *Theelin*, *Œstroform*, *Unden* and *Menformon*, in 0.05, 0.1, 0.3 and 1 mg. tablets also injections, ointmen suppositories.

2. **ŒSTRADIOLIS MONOBENZOAS** (*Oestradiol. Monobenz.*), Dihydroxyœstrin monobenzoate, Estradiol benzote, $C_{25}H_{28}O_3$; α -3-benzoyloxy-17-hydroxy- $\Delta^{1.3.5}$ -œstratriene.



May be prepared by the reduction of œstrone and benzoylation of the œstradiol produced. Inodorous, colourless crystals, insoluble in alcohol 95% but more soluble in fixed oils. One unit is the œstrus-producing activity contained in 0.0001 mg. of the standard preparation of dihydroxyœstrin

monobenzoate. Dose, 1/60 to 1/12 grain or 1 to 5 milligramme by intramuscular injection: 10,000, to 50,000 units daily.

Injectio Œstradiolis Monobenzoatis (*Inj. Œstradiol. Monobenz.*), See p. 45. Dose as of œstradiol monobenzoate. If the strength is not stated, 1 mg. in 1 ml. shall be dispensed.

COMMERCIAL PREPARATIONS are *Ovocyclin B*, *Progynon B*, *Dimenformon* and *Œstroform* (ampoule). *Œstradiol* is 20 mg. pellet for implantation.

3. ŒSTRADIOLIS DIPROPIONAS (*Œstradiol. Diprop.*), Dihydroxyœstrin dipropionate, $C_{24}H_{32}O_4$.

Œstradiol dipropionate is α -3 : 17-dipropionyloxy- $\Delta^{1\cdot3\cdot5}$ -œstratriene, prepared by the reduction of œstrone and propionylation of the α -œstradiol produced, by refluxing with propionic anhydride and sodium propionate and recrystallisation from aqueous acetone.

Colourless inodorous crystals, insoluble in water, slightly soluble in alcohol (95%) and soluble in acetone and in fixed oils. Dose, 1/60 to 1/12 gr. or 1 to 5 milligram (10,000 to 50,000 units) daily, intramuscularly.

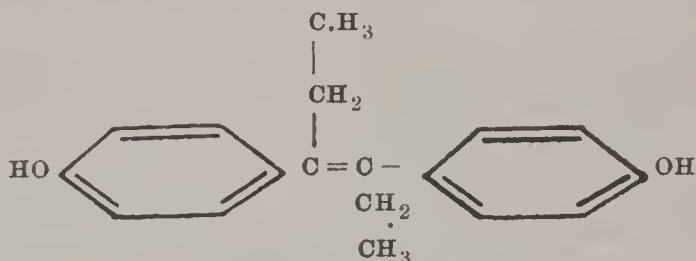
The unit is the specific œstrus producing activity of 0.0001 mg. of the standard preparation.

Injectio Œstradiolis Dipropionatis (*Inj. Œstradiol. Diprop.*), See p. 45. Dose as of œstradiol dipropionate. If the strength is not stated one containing 1/60 gr. in 15 min. or 1 mg. in a ml. is supplied.

COMMERCIAL PREPARATIONS.—*Ovocyclin P.*, *Dimenformon dipropionate* 5 mg. ampoules.

4. STILBŒSTROL (*Stibœstr.*), Diethylstilbœstrol, $C_{18}H_{20}O_2$.

This is 4 : 4'-dihydroxy- α : β -diethylstilbene and prepared synthetically. Contains not less than 99% of $C_{18}H_{20}O_2$.



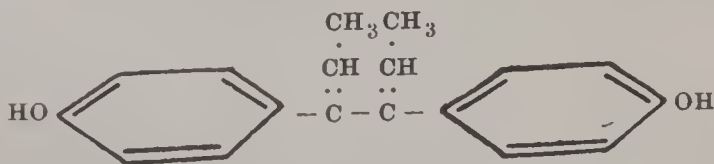
Colourless crystals or crystalline powder with a faint odour : very slightly soluble in water, readily soluble in alcohol (95%), solvent ether and in watery solution of alkali hydroxides.

Dose, 1/120 to 1/30 grain or 0.5 to 2 milligram daily.

Tabellæ Stilbœstrolis (*Tab. Stilbœstr.*), See p. 58.

COMMERCIAL PREPARATIONS are STILBŒSTROL, *Neo-œstranol* and *Cline-strol* in 0.5, 1 and 5 mg. tablets and *Stilbœstrol dipropionate* ampoule, 1 and 5 mg. each.

5. DIENŒSTROL (*Dienœstr.*), Diencestrol, $C_{18}H_{18}O_2$.



Diencestrol is prepared by dehydration of the pinacol obtained by reduction of *p*-hydroxypropiophenone.

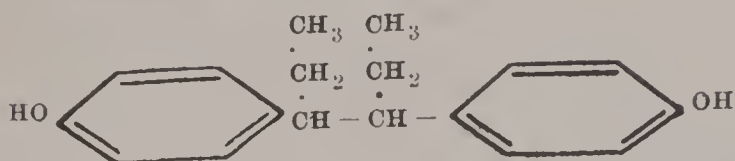
A colourless inodorous crystalline powder, almost insoluble in water, is readily soluble in alcohol (90%), in acetone and in solvent ether : soluble in watery solution of sodium hydroxide.

Dose, 1/600 to 1/12 grain or 0.1 to 5 milligrams daily.

Tabellæ Diencestrolis (*Tab. Dienœstrol.*), See p. 57. Contains between 89 and 110% of Diencestrol.

If quantity is not stated 0.1 mg. tablets are supplied.

Available in 0.1, 0.3, 1 and 5 mg. tablets and 2.5% ointment. *Neocline-strol* in 0.5, 1 and 5 mg. tablets.

6. HEXÆSTROL (*Hexæstr.*), Hexæstrol, $C_{13}H_{22}O_2$.

Hexæstrol may be prepared by the catalytic hydrogenation of the liquid form of diethylstilbæstrol dimethylether and subsequent demethylation of the product. It contains not less than 99% of $C_{13}H_{22}O_2$ dried at 100° .

Colourless, inodorous crystals or crystalline powder, insoluble in water, soluble in alcohol (95%), acetone and in solvent ether: dissolve in vegetable oils and in watery solution of sodium hydroxide.

Dose, 1/60 to 1/12 grain or 1 to 5 milligrams daily.

Tabellæ Hexæstrolis (*Tab. Hexæstrol.*), See p. 57. Each tablet contains 89 to 110% of $C_{13}H_{22}O_2$. Dose, as of Hexæstrol. Each tablet if not otherwise stated contains 1 mg.

7. PROGESTERONUM (*Progesteron.*), Progestin, $C_{21}H_{30}O_2$, Progesterone is 3 : 20-diketo- Δ^4 -pregnene.

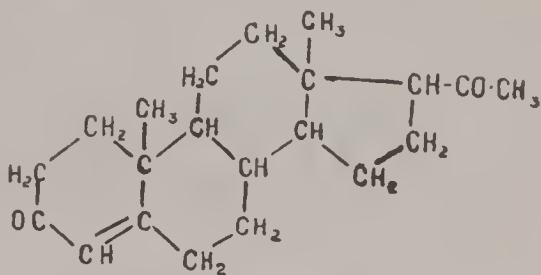
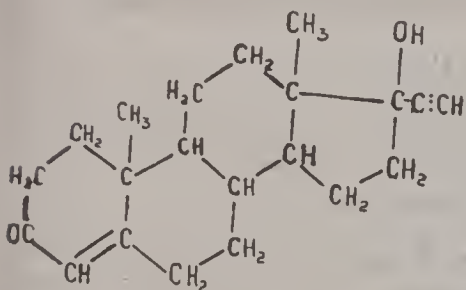
It may be prepared from the corpus lutea of the ovaries of sows and other mammals or from stigmasterol (a sterol found in soya beans), pregnanediol or cholesterol. One unit is 1 mg. of the standard preparation of progesterone.

Inodorous, colourless crystals, insoluble in water but readily soluble in alcohols, solvent ether, chloroform, benzene and fixed oils.

Dose, 1/30 to $\frac{1}{2}$ grain (2 to 20 units) or 2 to 20 milligrams by intramuscular injection daily.

Injectio Progesteroni (*Inj. Progesteron.*), See p. 46.

COMMERCIAL PREPARATIONS are *Lutocyclin*, *Lutren*, *Proluton*, *Luteostab*, *Lipo-lutin* and *Progestin*: 1, 2, 5 and 10 mg. ampoules and 100 mg. tablet for implantation.

8. ÆTHISTERONUM (*Æthisteron.*), Pregneninolone, Anhydrohydroxyprogesterone, Ethinyltestosterone, $C_{21}H_{28}O_2$.

Ethisterone is obtained by the addition of acetylene to the ketone group at position 17 in dehydro-*iso*-androsterone, obtained as a product of the degradative oxidation of sterols such as cholesterol and subsequent oxidation.

A white or creamy white almost inodorous tasteless, minutely crystalline powder: insoluble in water: very sparingly soluble in chloroform and in vegetable oils: soluble in hot acetone.

Dose, 1/12 to 2/5 grain or 5 to 2/5 milligrams.

Tabellæ Æthisteroni (*Tab. Æthisteron.*), See p. 57.

Dose, as of ethisterone.

If quantity is not stated, 5 mg. tablets are supplied.

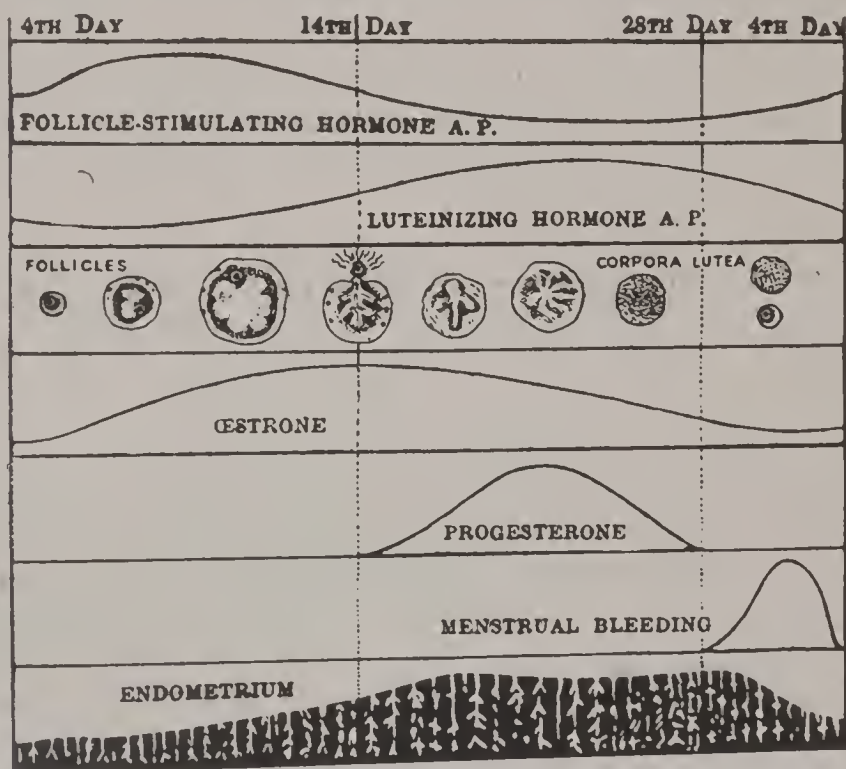
COMMERCIAL PREPARATIONS.—*Ethisterone*, 5, 10 and 25 mg. tablets: *Oraluton*, *Progestoral*, *Proluton C* and *Lutocyclin* in 5 or 10 mg. tablets.

Pharmacology [and Therapeutics]

(i) The natural hormones and their derivatives are *Estrone*, *Estradiol dipropionate* and *Estradiol monobenzoate* : one recently introduced is *Ethinyl œstradiol*. The synthetic hormones are *Stilbœstrol*, *Dienœstrol*, and *Hexœstrol* : these are **follicular**.

(ii) *Progesterone* is obtained both from natural source and synthetically and *Ethisterone* is synthetically prepared. These are **luteinizing**.

The therapeutic administration of these is usually one of substitution therapy and the effect lasts as long as the substance is there although some observers believe that by reciprocal stimulation of the anterior pituitary, occasionally some permanent restoration of function may be possible.



NORMAL MENSTRUAL CYCLE

Fig. 21.—From the 4th day after menstruation Anterior Pituitary hormone acts on the ovaries to make œstrone and cause ovulation on the 14th day : the progesterone phase is from the 14th to the 28th day at the end of which menstruation starts and lasts for 4 days.

The *Follicular hormone* is the real female sex hormone which is responsible for the normal development of the sex organs and the breasts, normal contraction of the uterus and menstruation also determines the female habitus and psyche. The *Luteal hormone* is almost entirely supplementary being necessary for implantation of the fertilized ovum and by relaxing the uterus, maintenance of pregnancy. This also probably influences carbohydrate metabolism.

The underlying principles for their therapeutic administration are as follows.

In a normal woman in puberty, at a certain time (usually starting from the 4th day after menstruation) an ovum within the follicle commences to mature. The follicle itself gets distended and is rich in follicular hormone (*œstrone*). This causes a marked thickening of the endometrium (proliferation phase). By about the 14th day, the maturation is complete, the follicle ruptures and the ovum is liberated which enters the Fallopian tube. The empty follicle is now filled with yellow lipid-containing cells (corpus luteum) and secretes a new hormone, *progesterone*. This converts the proliferated endometrium into a secreting mucosa with nutritive substances preparing it for the reception of the fertilized ovum. It also forms and maintains a decidua. If the ovum is not fertilized, it dies; the corpus luteum retrogrades, much hypertrophied endometrium breaks down and menstruation starts. This process is repeated regularly in about 28 days. These changes are governed by the follicle-stimulating, luteinizing and luteotrophic hormones of the *anterior pituitary*: the hormones immediately concerned are *œstrone* from the ovarian follicle and *progesterone* from the corpus luteum. During pregnancy, an enormous amount of follicular hormone is produced and excreted. This has no effect as long as corpus luteum hormone is sufficient to antagonize it, the latter being formed in a large amount from an additional site also, from the placenta. In case of intra-uterine death of the foetus or at the last month of pregnancy, the follicular hormone by acting on the posterior pituitary, starts labour.

A part of progesterone is conjugated into an inactive sodium pregnanideol glycuronate and excreted in the urine: its presence is therefore an indication of normal progesterone activity in the system. The other portion of it is probably destroyed in the liver.

For therapeutic purposes, *œstradiol* and *progesterone* need not be administered at the same time. These are given one at a time according to the physiological need of the ovary. Sometimes one may be followed by other in its respective phase to cause more intensive action.

Pregnancy urine contains *œstrone* and *œstradiol* excreted as esters of glycuronic acid. *œstrone* is more potent orally and *œstradiol* by injection. *Progesterone* is obtained from the ovary upto 3rd month of pregnancy and after this, this is produced from the placenta and obtained from pregnancy urine.

The synthetic hormones are cheaper and more easily available than the natural ones and are capable of oral administration.

Administration.—These may be given orally, introduced into the vagina to be slowly absorbed therefrom or given by *intramuscular injection* dissolved in an oil. Sometimes sterile

tablets are *implanted* in the subcutaneous tissue which maintains the effect for many weeks. *Linguets* and *ointments* are also used.

Pharmacology [and Therapeutics]

1. **ESTRONE.**—This has typical estrogenic function: therapeutic application is needed in the following: (i) conditions associated with *undeveloped puberty* (hypoplasia of the genitals and primary amenorrhœa): (ii) *menopausal syndrome* (vasomotor and psychological disorders): (iii) *localised affections* (senile vaginitis, vulvitis, kraurosis vulvæ, gonorrhœal vulvitis of children and hypoplasia of the breasts): (iv) *menstrual disturbances* (secondary amenorrhœa, spasmodic dysmenorrhœa and menstrual disturbance epilepsy): (v) in connection with *other glands disturbance* (inhibition of anterior pituitary and of lactation).

The selection of an œstrogen for any of these conditions depends on its solubility, absorption rate through various routes, mobilisation and excretion rate: also the nature of action required (immediate and intensive or slow and sustained for a prolonged period). On these considerations, parenteral, oral or local application of the substance in a varying dose is proposed.

œstrone may be administered *orally* in a dose at least 5 times of oily solution *parenterally*. *Inunction* of a cream, vaginal or rectal *pessaries* or *suppositories* and *implantation* of tablets are also sometimes necessary.

(a) For *menopause* 0.2 to 1 mg. parenterally once a week or more frequently and followed orally by 0.1 to 0.3 mg. daily. Disagreeable symptoms if appear, may require temporary suspension of treatment.

(b) In *menstrual disturbances*, orally 0.2 to 1 mg. daily for period corresponding to the normal menstrual cycle for 2 weeks or 0.1 to 1 mg. intramuscularly once or twice a week.

(c) For *kraurosis vulvæ*, orally 0.1 to 1 mg. daily or 5 mg. intramuscularly weekly may be given. For *gonorrhœal vaginitis*, 0.3 to 0.6 mg. orally daily and in either case, cream or pessary locally is also applied.

(d) To *inhibit lactation*, 15 to 25 mg. orally or 5 mg. intramuscularly in several divided doses, soon after delivery: also local application of the cream. To cause *breast development*, oral and local application are necessary.

(e) For delayed *puberty* and in *retarded growth* 0.1 increased to 1 mg. daily orally may be necessary.

2. **(ESTRADIOL MONOBENZOATE and DIPROPIONATE.**—These are given in oily solution intramuscularly. As these act after slow liberation from the site of injection, these are especially suitable for "depot" formation. (a) For *menopausal symptoms*, 1 to 5 mg. weekly: (b) for *delayed puberty*, 5 mg. every

2 weeks : (c) for *hypo-ovarianism* in a young woman, 5 to 10 mg. weekly ; (d) for *primary inertia* and delayed labour, 2 mg. hourly upto 10 hours.

ETHINYL ŒSTRADIOL (Not official), prepared from œstrone is given orally and effective in 0.01 to 0.02 mg. (sometimes 0.05 mg.) doses : does not cause disagreeable symptoms and on the other hand gives a sense of general well-being. Commercial preparations are *Ethidol*, *Lynoral*, *Dyloform*, *Estigyn*, and *Eticylin* (Linguetes are also available) : in 0.01, 0.05 and 1 mg. tablets. This is considered to be the œstrogen of choice.

ointments of œstrone (*Menoformon*) in tubes of 18 grm. containing 9 mg. of œstrone and of œstradiol benzoate, (*Dimenformon*) in tubes of 18 grm. containing 36 mg. of œstradiol monobenzoate are available : used by inunction in (a) senile *vulval changes* and in *dyspareunia* of the young (0.5 to 1 mg. daily) : (b) *Breast*, hyperlactation of puerperium (0.25 mg. once or twice daily) and hypoplasia (1 mg. daily on alternate sides) : (c) *Aone vulgaris* (0.25 mg. daily) : (d) *Alopecia*, *hypertrichosis* and *hyperkeratosis* (0.5 to 1 mg. daily). *Bougie Kolpon* Œstrone and *Supp. Menformon*. 0.1 mg. each.

3. STILBŒESTROL, the synthetic œstrogenic hormone is administered orally (available as tablets of 0.5, 3 and 5 mg.) used for the same conditions as œstrone. For *menopausal symptoms* 0.1 to 1 mg. 2 or 3 times daily and a larger dose for *senile vaginal conditions* : for inhibiting *lactation* 2 mg. 2 or 3 times daily may do. Bigger doses may cause nausea and vomiting.

STILBŒESTROL DIPROPIONATE is given by intramuscular injection : the effects are less intense but more prolonged. This has also been used in carcinoma of the prostate in 5 to 10 mg. daily for 5 to 10 days followed by 1 mg. stilbœstrol orally 2 or 3 times daily for 2 to 3 months.

4. DIENŒESTROL is less active than stilbœstrol : seldom causes nausea or vomiting even in big doses. It is used for the same conditions as stilbœstrol 0.1 mg. even up to 3 mg. 2 or 3 times daily orally : for carcinoma, bigger doses are necessary. Available in 0.1, 0.3, 1 and 5 mg. tablets and 2.5% ointment.

5. HEXŒESTROL in 1 to 5 mg. doses is given orally for stilbœstrol and is better tolerated. It may be given intramuscularly also in oily solution like stilbœstrol dipropionate for carcinoma of the prostate.

6. PROGESTERONE is therapeutically indicated for its lentinizing action in (i) functional *uterine hæmorrhage* of an inovulatory cycle or when corpus luteum formation is inadequate with undeveloped secretory phase of the endometrium : Dose is 20 mg. spread over 8 injections ending 3 days before the expected period. (ii) *Metropathia hæmorrhagica* : 10 mg. spread over 6 to 8 days ending not less than 3 days before the period : this treatment is repeated monthly till normal period appears. (iii) Impaired *fertility* or repeated *abortions* : 10 mg. divided in the above way and dose increased after a fertile coitus and continued for 6 to 8 weeks and then dose is gradually reduced. (iv) *Threatened abortion* : 10 mg. or more daily may help.

(v) *Secondary amenorrhœa, nidatory failure and abortion* (due to incomplete preparation of the endometrium) may require combined therapy : 12.5 mg. of progesterone with 2.5 mg. of œstradiol (available as *Disecron*) intramuscularly for 2 successive days. The treatment is repeated after 28 days, may be continued for about 6 months.

7. **ETHISTERONE** is a synthetic preparation for oral administration for progesterone action. This is used in habitual *abortion, sterility* and in menopausal *hæmorrhage* : one tablet of 5 or 10 mg. is taken sublingually or orally shortly before meal, once or twice daily : combined therapy with *orasecron* (10 mg. ethisterone and 0.05 mg. ethinyl œstradiol) one tablet for 5 days from the date of probable ovulation and repeated at the next estimated date of ovulation (this is about 12 to 16 days after the beginning of previous menstruation).

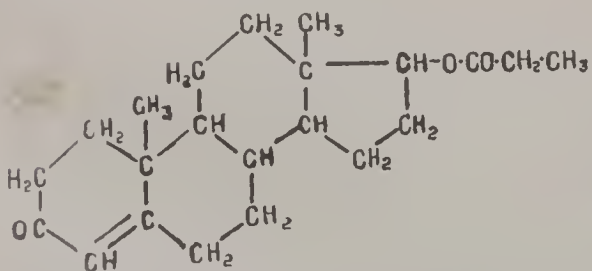
SUMMARY.—Female sex hormones : The *œstrogenic hormones*, natural and synthetic are meant for proper and adjusted menstruation and ovulation with timely growth of secondary sex characters. These are of some value in mammary and prostatic carcinoma. The *luteinizing hormones* are also either natural or synthetic and used for ensuring implantation of the fertilized ovum and its maintenance during pregnancy also control the quantity of menstrual bleeding. These are used orally, by intramuscular injection, ointment, pessary, suppository or implantation of sterile tablets.

B. Male Sex Hormones : Androgen

Male Hormones are of two kinds : (i) **gonadotropic** from the anterior pituitary and (ii) **gonadic** isolated from the testes (*testosterone*) and male urine (*androsterone*) also prepared synthetically from cholesterol (*testosterone* and *methyltestosterone*) the last being now more commonly used.

The gonadotropin is suitable in cases where the normal testicular tissue is present but requires activation : if this is absent as in a castrate, *testosterone*, is the only remedy. In such cases it is only a substitution therapy (like insulin or thyroxine) a maintenance dose being required life-long.

1. **TESTOSTERONI PROPIONAS** (*Testosteron. Prop.*), 17-pionoxy- Δ^4 -androsen-3-one, $C_{22}H_{32}O_3$.



Testosterone propionate may be prepared by the action of propionic anhydride on testosterone which is prepared from testis or from dehydro-*isoandrosterone*, an oxidative degradation product of cholesterol.

A white or creamy white, inodorous, crystalline powder, insoluble in water, soluble in alcohol (95%), in acetone and in fixed oils.

DOSE, 1/12 to 2/5 gr. or 5 to 25 milligram, intramuscularly.

Injectio Testosteroni Propionatis (*Inj. Testosteron. Prop.*), See p. 47

DOSE as of Testosterone Propionate by intramuscular injection. If the strength is not stated, one containing 1/6 gr. in 15 min. or 10 mg. in 1 ml. is dispensed.

COMMERCIAL PREPARATIONS are *Perandren*, *Testoviron*, *Neo-hombreol* and *Erugon-S* in 5, 10, 25 and 50 mg. ampoules: also ointment and suppository. *Pellets* of Testosterone, 100 mg. for implantation.

2. METHYLTESTOSTERONUM (*Methyltestosteron.*)

Methyltestosterone, $C_{20}H_{30}O_2$, is prepared by oxidation of 17-methyl- Δ^5 -androstene-3:17-diol, obtained by the action of methyl magnesium iodide on dehydro-*iso*-androsterone, a product of the oxidative degradation of cholesterol.

A white or creamy white, inodorous, tasteless crystalline powder insoluble in water, soluble in alcohol (95%), acetone and in fixed oils.

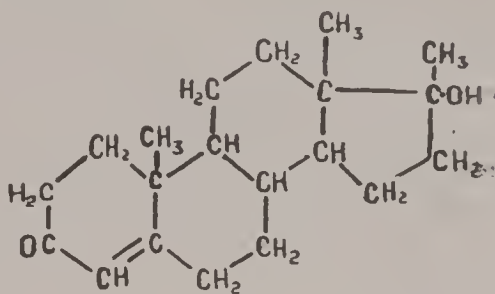
Dose, 2/5 to $\frac{3}{4}$ gr. (1/12 to $\frac{1}{3}$ gr. in women) or 25 to 50 milligram (5 to 20 milligram in women) daily.

TABELLÆ METHYLTESTOSTERONI (*Tab. Methyltestosteron.*), may be prepared by moist granulation and compression.

Dose as of Methyltestosterone.

If the quantity is not stated, 5 mg. tablets are supplied.

Available in 5, 10, 25 and 50 mg. tablets.



Pharmacology [and Therapeutics]

Testosterone normally mediates the development of male-accessory sex glands (penis and prostate), pubic hairs and beard and lowering of the voice, the characteristics of **puberty in man**.

Testosterone increases the **basal metabolism** (up to 40%) without a rise in the temperature. It exerts a **mild sodium retaining action** which may favour water-retention. Further it appears to speed up certain processes of **bone development** before the epiphyses are closed. There is action on the **skeletal muscles** causing retention of nitrogen, potassium, phosphates and also probably other building materials causing (compared with a female) an increase in the mass of skeletal tissues, proteins store and the body weight. A man usually thus has a bigger body.

Testosterone tends to **inhibit the oestrogens** in the female and persisted in bigger doses in them, may have some masculinizing effects.

It appears that in therapeutic application, a *male is directly* benefited by androgens and a *female indirectly* by lessening ovarian hyperfunction. Antagonistic action is seen in a castrated rat; oestrus is produced by daily injection of oestron: this is inhibited by simultaneous administration of testosterone.

In addition, certain synergism appears also to be present. Thus simultaneous administration of androsterone and oestron causes more rapid increase in the weight of the prostate and seminal vesicles in a rat.

(i) *In a male* the endrogens are therapeutically used in delayed development of the secondary sex characters (**eunuchoidism**) in the male. In primary hypogonadism, only testosterone and in secondary cases, this as well as anterior pituitary hormone at least in some cases, are necessary. Impotence and sterility are often markedly benefited although spermatogenesis is not directly effected. **DOSE**, 5 to 25 mg. twice weekly.

Cryptorchidism (undescended testes) sometimes, and prostatic hypertrophy occasionally, improve.

Androgens are sometimes used (a) in the elderly males for certain nervous symptoms as vertigo, nausea, nervousness and insomnia (**male climacteric**) : (b) to stimulate **metabolic activities** in severe emaciation as in hyperthyroidism and in premature babies and (c) in *angina pectoris*.

(ii) *In the females*, menorrhagia and inter-menstrual hæmorrhage and mastitis are sometimes treated with testosterone alternatively with œstradiol and progesterone. Such combination is said to be more effective. But the dose of testosterone should not exceed 150 to 300 mg. per month otherwise some masculinization may follow.

DOSE, 10 to 50 mg. of Testosterone propionate intramuscularly two or three times a week according to the deficiency are usually required. For oral administration, Methyl testosterone tablets 10 mg. or more : for subcutaneous implantation, 75 mg. testosterone are prescribed.

SUMMARY.—Male sex-hormones : *Testosterone* and *Androsterone* stimulate the formation of **male sex-hormone** and are indicated in deficiency state : in the female these may be used to inhibit hyperactive **œstrogenic hormone**.

MALE SEX-HORMONES.—*Testosterone Propionate* or *Testoviron*, *Neo-hombreol* ampoules 5, 10 and 25 mg. in 1 c.c. *Methyl Testosterone*, *Neo-hombreol (M)* or *Oraviron* tablets 5 and 10 mg. each orally. *Erugon* 1 c.c. intramuscularly or pellets orally : *Viriligen* 1 c.c. ampoules or tablets (oral) : *Androstin* 10 c.c. ampoules or tablets (oral). *Perandren* (synthetic) containing 5, 10, 25 and 50 mg. in oil intramuscularly also *Linguets*. *Ointments* and *suppositories* are also available.

POSTERIOR LOBE EXTRACT

(i) **Injectio Pituitary Posterioris** (*Inj. Pituit. Post.*), Pituitary (Posterior Lobe) Extract.—See p. 46. It is a clear colourless liquid with a faint odour. Sterilised by *filtration* before putting in the ampoule or by *autoclaving* after sealed in the ampoule. **DOSE**, 3 to 8 minims or 0.2 to 0.5 ml. (2 to 5 units) by subcutaneous or intramuscular injection.

(ii) **Injectio Oxytocini** (*Inj. Oxytoc.*), See p. 45. It contains 10 units per ml. : a clear colourless liquid.

Reaction lies between pH 3 and 4. Potency is kept up for 1½ year.

DOSE, 8 to 15 minims or 0.5 to 1 ml. (5 to 10 units) subcutaneously or intramuscularly.

(iii) **Injectio Vasopressini** (*Inj. Vasopress.*), Vasopressin. See p. 48. It contains 10 units per ml. **DOSE**, 8 to 25 minims or 0.5 to 1.5 ml. (5 to 15 units), subcutaneously or intramuscularly.

Pharmacology [and Therapeutics]

The posterior (nervous) portion of the Pituitary body contains a powerful and stable internal secretion which is frequently used.

Therapeutically the main uses of posterior pituitary fractions are as *uterine* and *intestinal muscular stimulant* and *antidiuretic*.

By intravenous injection of posterior pituitary extract, it was found that it causes contraction of the *unstriated muscle fibres* including those of the blood vessels (Oliver and Schaefer, 1795). Next, *oxytocic action* on the pregnant uterus was found (Dale, 1906) and after this, *antidiuretic action* (Velde, 1912).

The pituitary stalk, isolated from nervous connections by cutting through the spinal cord and the splanchnics also cut, electrically stimulated, is capable of causing uterine contractions: this shows that pituitary activity is *hormonic* and not nervous.

The posterior pituitary contains **two active principles**; the first, the **pressor**, raising the blood pressure and maintaining the tone of the intestinal muscles, especially of colon and is **antidiuretic** also: the second, the **oxytocic**, contracting the uterine muscles. These two are available in separate forms so that the oxytocin (*pitocin*) only favours the contraction of uterus without raising the blood pressure and the vasopressin (*pitressin*) is indicated in surgical shock associated with considerable fall of blood pressure and also in post-operative intestinal paresis.

The action is best shown when the extract is given intravenously, and also fairly well when given subcutaneously. A slight systemic effect is also obtained from application on the nasal mucous membrane and less so when given per rectum but none from an oral administration as the gastric enzymes destroy it. Its main action is **directly on the involuntary muscles** and not on any nervous structure, either at its anatomical end or at the myoneural junction.

CIRCULATION.—(i) The peripheral *arterioles* are constricted. In an animal, the skin and the mucous membrane become markedly pale lasting for a few minutes or more. After a brief abrupt fall, the **blood pressure is raised** but this is smaller, slower and more lasting than that following the administration of adrenaline hydrochloride. Both the systolic and the diastolic pressures are raised, lessening the pulse pressure. It does not affect the arteries according to their vaso-motor innervation, constricting all arterioles including the pulmonary and the coronary vessels because the action is *direct on the wall of the blood vessels*. It does not constrict the renal arteries, which are even more dilated. The slight initial fall of blood pressure is probably due to the spasm of the coronary blood vessels causing temporary myocardial depression; sometimes

delayed auriculo-ventricular conduction may result from the same cause.

In a person with coronary arteriosclerosis, an injection of pitressin may cause such coronary vasoconstriction and myocardial depression that profound circulatory collapse and even death may follow. A barbiturate given along with it may aggravate the effect.

(ii) The **heart action** is quickened temporarily during the stage of drop in the blood pressure but soon it is slowed partly for the direct action on the muscles (an excised and isolated heart is also slowed) and partly for stimulation of the medullary centre (inhibitory mechanism) caused by increased blood pressure. The cardiac output is markedly reduced altering the T-wave in the electrocardiogram. If a second injection is given a few hours after the first, there is no further rise and even may be actual fall. So it is not usually repeated within 12 hours of the first dose. [It is sometimes given hypodermically or intravenously in many conditions of lowered blood pressure as in surgical shock, acute infective fever and in cholera].

OTHER PLAIN MUSCLES are also powerfully contracted.

(i) **INTESTINE.**—The muscles are powerfully contracted with **increase of tone** and diminution of relaxation. This effect is more marked with pitressin than with oxytocin. [Pitressin and sometimes the whole posterior pituitary extract is given in the atonic condition of the bowels with gaseous distension of the colon and constipation especially following an abdominal operation. The effects are produced in 5 minutes and maintained for the next 1 to 1½ hours. Pitressin in 2 doses of 0.5 c.c. is given intramuscularly half hour before taking a skiagram of the bile passages and the kidneys: the intestinal gas being expelled, a clear picture is obtained].

(ii) **UTERUS.**—Posterior pituitary extract and especially the oxytocic fraction causes **powerful contraction** of the uterine muscles with diminished relaxation and this is more marked than that of any other plain muscle. This action is direct on the muscles. An isolated uterus in warm saline bath containing the pituitary extract, shows marked contraction whether pregnant or not. But in an intact animal and in a human being this is more obvious in the first two weeks of menstrual cycle and also in later portion of pregnancy, the effects being controlled by the specific actions of the anterior pituitary and the ovarian hormones. The pregnant uterus is more powerfully acted on, especially when this is already contracting during labour. This action is so dependable for therapeutic purposes that it ranks second only to ergot, being prompt, less violent but less lasting than that of ergot. [It is therefore often utilised in delayed labour without obstruction, after the full dilatation of the os, and is hence called the "**medical forceps**". It is also of use immediately after delivery in ½ to 1 c.c. dose along with ergometrine to control postpartum hæmorrhage].

The effect of *oxytocin* is to cause contraction of the uterus followed by increased activity. This of *pitressin* is contraction followed by diminished activity due to uterine vaso-constriction. The effect of the *whole extract* is contraction of the organ and occasionally depression at the later stage. (Morgan).

(iii) URINARY BLADDER.—This also contracts powerfully emptying out its contents more completely.

(iv) MAMMARY GLANDS.—The pituitary ext. increases the secretion of milk, but it is an **indirect galactagogue**, increasing the flow by powerful contraction of the muscles of the gland. It is not used therapeutically for this purpose.

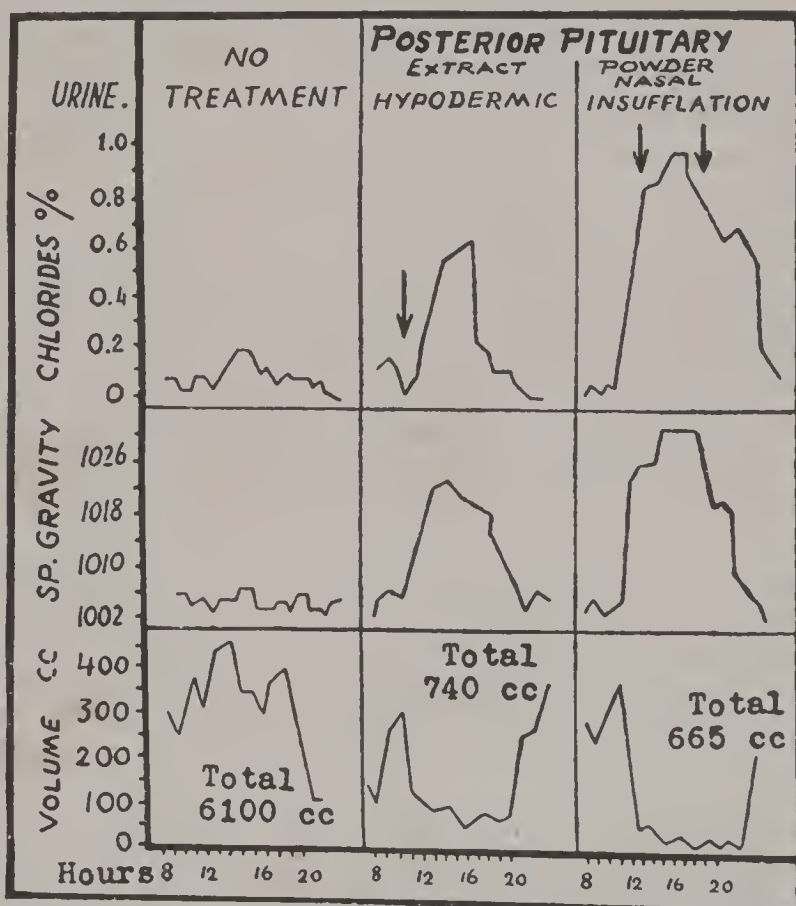


Fig. 22.—The action of Posterior Pituitary Extract on the kidneys. In deficiency, the chloride contents and specific gravity of urine fall but its volume increases : reversed in its therapeutic administration.

RESPIRATION.—It acts centrally, causing by vasoconstriction alteration of blood supply to the medullary centres. The respiration usually becomes fuller and deeper and afterwards slower and shallower. After an intravenous injection, an unanæsthetised animal shows periods of **apnoea** alternating with **exaggerated breathing**. The purified extract without histamine contamination does not cause any broncho-constriction.

KIDNEYS.—An anæsthetised rabbit shows increased diuresis, due to better renal circulation and contraction of the efferent

arterioles, raising the glomerular pressure. This is followed by a stage of diminished urinary secretions which may continue for some time. But in the human being and in unanæsthetised animals, the urinary secretion is lessened, without any period of diuresis, probably due to increased water reabsorption from the renal tubules but not due to any vascular or nervous cause. It will thus inhibit water diuresis but not salt, urea or xanthine diuresis as these are not reabsorbed. [Vasopressin is of great value in 2 to 10 units doses daily in diabetes insipidus, a condition associated with profuse watery urination. But the beneficial effects are short-staying; remain as long as the drug is administered]. In order to avoid frequent injection, dry powder of pitressin has been insufflated into the nose or pitressin tannate in oil 0.5 to 1 c.c. containing 5 to 10 units, is given by intramuscular injection once daily.

METABOLISM.—It favours glycogenolysis and hyperglycæmia probably by the action of oxytocin on the liver [so is useful for the treatment of hypoglycæmia from an overdose of insulin]. Other effects are probably vascular. During the stage of feeble cardiac activity, oxygen consumption is lessened, CO_2 tension is lowered and lactic acid accumulates in the blood but these disappear as soon as the circulation improves.

NERVOUS SYSTEM.—It has no action but very big doses increase the quantity of cerebro-spinal fluid from direct action on the choroid plexus and cause sleepiness and muscular weakness.

In $\frac{1}{2}$ to 1 c.c. doses daily intramuscularly in the early stage of *herpes zoster* may relieve pain and shorten the course of the disease.

EXCRETION.—Most of the hormone is destroyed in the tissues and the remainder is slowly excreted by the kidneys.

THE INTERMEDIATE PORTION causes darkening of the skin of the frog by a melanophore stimulating substance but has no practical therapeutic value.

SUMMARY.—The posterior pituitary extract causes increased contraction of the unstriated muscles of the uterus especially when pregnant (*oxytocin*), of the intestinal and peripheral vascular musculature (*vasopressin*) and is antidiuretic especially in diabetes insipidus.

NON-OFFICIAL COMMERCIAL PREPARATIONS

PITOCIN and **ORASTHIN** (oxytocic): **PITRESSIN** and **TONEPHIN** (vasopressic and stimulates intestinal peristalsis), are the separated hormones of the posterior pituitary, given subcutaneously in $\frac{1}{2}$ to 1 c.c. doses as necessary. **ADRENO-PITUITARY: EVATMINE.**—Each c.c. contains $\frac{1}{2}$ of each of adrenaline solution and posterior pituitary extract are useful in bronchial asthma.

THYROID GLAND

THYROIDEUM (*Thyroid*). Dry thyroid, Thyroid extract. A cream-coloured amorphous powder with a faint meat-like taste and odour, prepared from the thyroid gland of ox, sheep or pig. The gland is dried at a temperature not above 60° , powdered, all fat removed with light

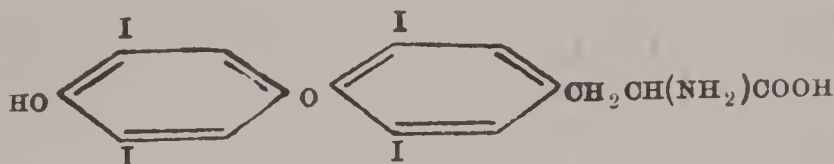
petroleum and the residue dried. It is *standardised* by its iodine contents which must be 0.1% (between 0.09 to 0.11%) in combination as *thyroxine*.

Dose, $\frac{1}{2}$ to 2 grains or 0.03 to 0.12 gramme (30 to 120 mg.).

Tabellæ Thyroidæ (Tab. Thyroid.), See p. 58. Dose as of thyroid. Each tablet if not otherwise stated, contains $\frac{1}{2}$ gr.

Pharmacology [and Therapeutics]

Thyroid gland contains a colloid material in combination with protein (*thyroglobulin*). Its active principle is *thyroxine* isolated by Kendall in 1915 with an empiric formula of $C_{15}H_{11}O_4NI_4$ which contains over 60% of iodine and this is the only tissue in the body that contains iodine. Its sodium salt called thyroxine sodium, has been prepared.



RECENT ADVANCES especially with the help of radio iodine showed the steps in the biosynthesis of thyroxine. Iodine is liberated from iodide ingested, by an enzyme oxidizing system (Harington, 1947). This iodine gets bound to the cytoplasm of the thyroid cells forming thyroglobulin. With iodine ammonia, tyrosine present there, is changed to mono-iodotyrosine (Fink, 1948 and Taurog, 1949) and then to diiodotyrosine and finally to thyroxine. Anterior pituitary thyrotropic hormone is the controlling agent for this and cellular hyperplasia.

Iodine administered to thyroidectomized rats, organic iodine upto 30% could be obtained and this was found to contain both diiodotyrosine and thyroxine. Thus metabolic activities which occur in the absence of thyroid, may be due to this extra-thyroid thyroxine. A protein as caseine rich in tyrosine by iodination may form a product containing thyroxine up to 1.7% (De Gennes and Deltour, 1948) and this in myxœdema is said to have beneficial therapeutic effect.

Administration of big doses of iodides to rats was found to inhibit iodoprotein formation in the thyroid gland and consequently formation of thyroxine (Wolff and Chaikoff, 1948) : this may throw some light on the inhibitory action of iodine in ex-ophthalmic goitre.

The anterior pituitary thyrotropic hormone stimulates the thyroid to secrete thyroxine which if reaches a certain level, inhibits the pituitary and brings in a mutual adjustment. In case of thyroid deficiency, the pituitary hormone is secreted in a larger amount, apparently for compensation. Further, hyperthyroidism causes other manifestations the some of which have resemblance to suprarenal stimulation.

Of a total of about 15 mg. of iodine present in the normal human thyroid, 0.5 to 1 mg. is destroyed daily. Iodine is

necessary for its replacement and this is obtained from the minute quantity of it present in the food : some of the inhabitants of the iodine poor locality may have the deficiency and get goitre. Thyroid increases the metabolic rates of nearly all cells (**calorigenic action**) : thus this is an essential requirement for normal bodily growth.

ACTION.—Desiccated thyroid gland given orally usually has no marked action on the normal person unless given in a very big dose. Repeated smaller doses produce symptoms more readily but takes near about ten days. Administration by intravenous injection also does not cause any marked immediate effect.

Although iodine is the chief constituent of thyroxine, this has very little iodine action, its main action being **hormonic**. It has a very remarkable power of increasing the **metabolic rate** shown by the raised body temperature, loss of weight, increased respiration, quickened pulse, increased secretion of urine and also heightened nervous irritability.

Thyroxine is the only remedy for all kinds of **thyroid deficiency** and it can be given by the mouth in the form of the desiccated gland-substance, without being affected by peptic digestion and is readily absorbed. The result is so remarkable that this is the best example of successful replacement therapy.

Marked thyroid deficiency in a child is called “**cretinism**” and in an adult, “**myxœdema**” and also some types of **goitre**. The deficiency is manifested by cold, dry, thick skin with an increase of subcutaneous fat and connective tissue. The face looks swollen, the body is unshapely, the hands and the feet become thick and hairs get scanty. The tongue is big and partly protruded with saliva trickling down the corners of the mouth. The muscles are flabby and the mental condition is poor. The basal metabolic rate falls, which may be about 60% of normal when the thyroid secretion is much low.

Such people, with a progressively increasing repeated doses of thyroid gland, remarkably improve, although slowly, both physically and mentally. The changes are manifested as follows :

Certain *symptoms of discomfort*, may be felt in the first few days as headache, pains and aches, nausea, vomiting and diarrhoea and some signs of increased metabolism. The disagreeable symptoms however disappear in a week or so. After a period which may extend up to 10 days, obvious clinical improvement is seen.

The *metabolism* is markedly increased with an all round improvement of the bodily functions. The urine contains a larger amount of protein waste products in the form of nitrogen, sulphur and phosphorus. The quantity of urine also increases due to greater elimination of urea. The intake of oxygen and output of carbon dioxide are increased and as a result of greater

internal combustion, body weight falls. There is more combustion of fat than of protein, the latter being only 1/16th of the waste. The carbohydrate metabolism is also increased. Glycogen diminishes from the liver and the blood sugar level rises so much so that there may be even be glycosuria. Calcium metabolism is also altered, there being increased calcium excretion.

Calcium elimination is low in myxœdema but high in thyrotoxicosis.

As a result, within a short time the individual looks very much like normal but as the benefit lasts as long as the drug is continued, its administration must be kept up practically life-long although usually in reduced doses.

A normal growing animal with thyroid treatment does not much increase in size or in weight but some of the viscera as the heart, liver, kidneys, pancreas and the suprarenals grow more rapidly.

Desiccated thyroid gland is also sometimes administered to reduce **constitutional obesity**. In order to produce a decided effect, big doses are often necessary. But this may cause severe toxic symptoms and is not to be recommended.

KIDNEYS.—Thyroxine causes **diuresis** probably by mobilising sodium chloride and water causing hydræmia. As this takes place fairly early this cannot be wholly the after-effect of increased metabolism and increased excretion of urea. The urine has a larger percentage of sodium chloride, urea, calcium and phosphates.

Thyroid gland is also sometimes useful in many chronic **skin diseases** especially those associated with dry thickened skin and falling off of hairs and also in various kinds of scaly eczema and psoriasis.

Its administration is indicated not only in myxœdema, some types of goitre and in cretinism but also in some cases of premature loss of hair, delayed union of a fractured bone²⁶⁵, high blood pressure, dry, scaly eczema²⁶⁶ and in chronic nephrosis.

The *dose* is adjusted in consideration of the intensity of deficiency and age. In a *cretin* of 6 months, the average dose is 6 mg. (1/10 gr.), increased to 60 even 120 mg. (1 to 2 gr.). In adult, with *myxœdema*, the starting dose is ½ to 1 grain (30 to 60 mg.) of the dried gland substance or 0.1 to 0.2 mg. of thyroxine sodium, 2 or 3 times daily, preferably on empty stomach and the dose is kept on for a few days for the full effect to develop: then, if necessary, this is gradually increased till the limit of tolerance is reached, marked by increased heart rate. Thyroxine has cumulative action and the effect tends to persist.

(265) R
Thyroideum gr. 1
Calc. Lact. gr. 15
Pulv. Twice daily.

(266) R
Thyroideum gr. ½
Ferr. Arsen. gr. 1/16
Glycer. Trag. q.s.
Pil. Twice daily.

SUMMARY.—Therapeutic administration of desiccated thyroid causes marked effect in thyroid deficiency (*cretinism* and *myxædema*) but not as much in a normal person. With graduated doses, after an interval for about 10 days, there is marked increase of general metabolism and considerable clinical improvement. A maintenance dose is kept up fairly long. *Signs of overaction* are to be watched for.

AVAILABLE as *Tablets thyroid*, 1/5, 1/3, 1/2 and 1 gr. and *Thyroxine sodium* 0.05 and 0.1 mg. each.

HYPERTHYROIDISM.—With a progressively increasing dose of thyroid gland, signs of overaction and intolerance are sometimes produced. The intensity manifests individual peculiarity. These are—

(i) *Heart.*—Pulse rate increases (tachycardia) and it becomes feeble. This is probably due to direct action on the heart muscles.

(ii) *Alimentary System.*—Nausea, vomiting, diarrhœa and disinclination for food appear.

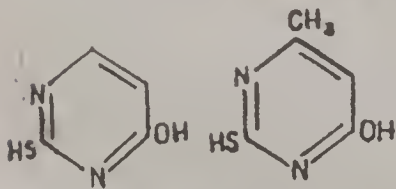
(iii) *Nervous System.*—Fine tremors, headache, restlessness, slight rise of temperature and increased perspiration. There may be a certain amount of dilatation of the pupil, widening of the palpebral fissure and prominence of the eye-ball. There is progressive weakness and loss of flesh and finally death takes place from asthenia.

When these appear, either the dose should be reduced or its administration stopped for the time being.

ANTITHYROID PRODUCTS

In certain diseased conditions especially in *Exophthalmic Goitre (Graves' Disease)*, the thyroid secretion is pathologically increased and drugs are sought for to lessen this or mitigate the symptoms of distress. Iodine has some effect (p. 160) and quinine is given in some cases (p. 342). More direct and powerful antithyroid preparations are *Thiouracil* and *Methylthiouracil*.

THIOURACIL (*Thiouracil.*), $C_4H_4ON_2S$.



Thiouracil Methylthiouracil

Thiouracil is 2-mercapto-4-hydroxypyrimidine and prepared by condensation of the sodium derivative of ethyl formylacetate with thiourea. It contains not less than 99% of $C_4H_4ON_2S$.

A white or cream-coloured inodorous powder with a bitter taste: very slightly soluble in water, in alcohol (90%), in ether and in acids. Readily soluble in dilute

watery solution of sodium hydroxide.

DOSE, 1½ to 3 grains or 0.1 to 0.2 gramme.

Tabellæ Thiouracilli (*Tab. Thiouracil.*), See p. 58. DOSE as of thiouracil. Each tablet if not otherwise stated contains 0.1 g.

METHYLTHIOURACILUM (*Methylthiouracil.*), $C_5H_6ON_2S$.

Methylthiouracil is 2-mercapto-4-hydroxy-6-methylpyrimidine, prepared by condensation of ethyl acetoacetate with thiourea: contains not less than 99% of $C_5H_6ON_2S$.

A white or pale cream inodorous powder with bitter taste : very little soluble in water, alcohol (95%) and in dilute mineral acids : readily soluble in dilute sodium hydroxide solution in water.

Dose, $1\frac{1}{2}$ to 3 grains or 0.1 to 0.2 gramme.

Tabellæ Methylthiouracilli (*Tab. Methylthiouracil.*), See p. 57. Dose, as of Methylthiouracil.

Each tablet if not otherwise stated, contains 0.1 g.

Pharmacology [and Therapeutics]

Thiouracil given orally has been found effective in conditions of thyrotoxicosis by diminishing the production of thyroxine (Astwood, 1943). This seemed to act by blocking the normal iodination of tyrosine concerned in the production of diiodotyrosine and thyroxine (depression of the peroxidase enzyme system) although inorganic iodine is absorbed. This produces an excess of pituitary thyrotrophic hormone causing hyperplasia of the thyroid gland and a certain amount of exophthalmos although other symptoms of thyrotoxicosis are controlled. See p. 405.

So in therapeutic administration of thiouracil, in **thyrotoxicosis**, although the basal metabolism is brought down near to normal often the thyroid gland does not reduce in size and exophthalmos remains nearly unchanged. If the patient is already on iodine treatment, the response to the drug is slow probably due to previously formed stored thyroxine with any that may now be formed, is keeping up thyrotoxicosis. If thyroidectomy is contemplated, thiouracil should be temporarily stopped (the hyperplasia of the gland may cause much bleeding) and Lugol's iodine solution is administered for 1 to 2 weeks immediately before the operation.

Thiouracil is readily absorbed from the alimentary tract and reaches the highest concentration in the blood in half an hour : the elimination is also fairly rapid. So the total daily dose is subdivided into 3 to 4 portions.

Dose, maximum, is 0.6 g. daily in 3 or 4 divided doses and gradually reduced : when the basal metabolism is reached normal, 0.05 to 0.1 g. daily, every other day or even less frequently (maintenance dose) may do.

Methyl Thiouracil is easier to produce and cheaper than thiouracil. It is equally effective and less likely to cause toxic symptoms. The patient may not be strictly kept in bed, a small dose of phenobarbitone being given as a general nerve sedative. The initial dose is 0.3 g. daily but the maintenance dose is smaller, 25 mg. even 15 mg. twice a week.

Propylthiouracil may be used in 100 to 150 mg. dose daily during the active stage and 50 to 75 mg. daily as the maintenance dose. Probably it is less toxic than thiouracil. Before subtotal thyroidectomy, a continued treatment with propylthiouracil and iodine gives better result.

Average duration of treatment is 8 to 9 months and follow up treatment for 9 to 10 months. In some cases, exophthalmos may disappear and goitre becomes less. If the treatment is stopped too soon, relapse may occur.

Thiouracil has also been used in the treatment of **heart conditions** as congestive heart failure, auricular fibrillation and angina pectoris.

TOXIC SYMPTOMS are drug fever, various skin lesions as dermatitis, urticaria and prurigo : œdema of the feet : arthritis or arthralgia : enlargement of the lymph glands and splenomegaly : cardiac arrhythmia and bradycardia which may be fatal : photophobia and conjunctivitis. But most important complication is *agranulocytosis* which may appear suddenly even with a moderate dose. So sore-throat with high fever should be considered as a danger signal.

Treatment.—Weekly blood examinations are essential. Vitamin B complex or proteolysed liver are good preventives : with obvious lowering of granulocytes, further administration should be immediately stopped.

SUMMARY.—*Thiouracil*, *Methylthiouracil* and *Propylthiouracil* are used orally for **pathological hyperthyroidism** : a *maintenance dose* is necessary after control of the active manifestations. *Toxic actions* are to be guarded against.

COMMERCIAL PREPARATIONS.—*Thiouracil* and *Methylthiouracil* are as tablets of 0.05 g., 0.1 and 0.2 g. *Propylthiouracil* is obtained in 25 mg. tablets.

PARATHYROID GLANDS (Not Official)

The Parathyroid Gland Hormone stabilizes the functions of the nervous system and raises the blood calcium level and also maintains calcium phosphorus balance without altering their absorption and elimination. The extra calcium that accumulates in the blood is probably obtained from stores already existing in the system, both in the soft tissues and in the bones. So the signs of *hypoparathyroidism* are (i) hypocalcæmia (lowered from the normal of about 10 mg.%), (ii) hyperphosphatæmia, (iii) lowered excretion of Ca and P and (iv) actual or potential tetany. *Hyperparathyroidism* is characterised by (a) hypercalcæmia, higher than 15 mg % is dangerous, (b) hypophosphatæmia, (c) large excretion of Ca and P in the urine exceeding what taken in food, (d) lowered blood volume and renal failure and (e) muscular weakness and hypotonia with loss of appetite, vomiting and diarrhœa : finally coma develops ending fatally.

This is obtained as *Liquor Parathyroidei U.S.P.*, *Parathormone* or *Paroidin* : this per unit raises blood calcium by about 1 mg.

It is frequently prescribed in many conditions associated with diminished calcium in the blood as *tetany*. This is also useful in lead poisoning ; lead deposited comes out along with calcium. (See p. 273). It must be given parenterally.

Repeated administration for a long time may cause cumulative poisoning and signs of hyperparathyroidism may appear.

The parathyroid hormone is of no use when a more intensive calcifying action is desired as in rickets, tubercular disease or a slowly healing fracture of a bone. (In the latter conditions, calcium should be given with Vitamin D.

One unit of Collip is 1/100th of the quantity required to raise the blood calcium of a dog weighing 20 kg. by 1 mg. per 100 c.c. within 16 to 18 hours.

DIHYDROTACHYSTEROL, A.T, 10. has parathyroid action. See p. 284.

INSULINUM, Insulin

Insulin is a preparation containing the specific antidiabetic principles of the mammalian pancreas.

The fresh or frozen pancreas is minced and extracted repeatedly with alcohol (95%) and from this the active substance is precipitated in the form of a dry powder. This is either made into solution containing 20 units of insulin per ml. or 10 units into sterile tablets. This is *standardised by biological assay*. Three units, given subcutaneously, should lower the blood sugar of a fasting rabbit weighing 2 kg. from 0.15 to 0.45% causing coma and convulsion. One unit is 0.0455 mg. of standard insulin hydrochloride.

A clear and colourless liquid free from turbidity or deposit. Tablets are easily soluble in water.

The stock should be kept at a temperature not above 20°. This maintains the potency for two years from the date of manufacture. The label should state this date.

The active extract was first prepared by Zuelzer (1907 to 1912) which caused lowering of blood sugar in depancreatized dog and also in diabetic patients but caused such toxic symptoms (probably hypoglycæmic shock) that it was considered unsuitable for general use. Murlin (1913 to 1916) also prepared the substance but failed to achieve the final step and this was done by Banting and Best (1922). Abel (1926) first prepared it in pure crystalline form and suggested the formula of $C_{12}H_{22}O_{17}N_4S_2H_2O$.

OFFICIAL PREPARATIONS.—(i) *Injectio Insulini (Inj. Insulin.)*, Insulin. See p. 44. A clear colourless liquid without any deposit. It is soluble in 80% alcohol: easily destroyed by alkalies but more stable in acid solution. It contains in one ml. 90 to 110% of the stated amount. Dose is as determined by the physician according to the need of the patient, to be given by injection. Usually 20 units per ml. is dispensed.

(ii) *Injectio Insulini Protaminati cum Zinc* (*Inj. Insulin. Protaminat. c. Zinc.*), Protamine zinc insulin. See p. 44. Almost colourless, turbid liquid. Reaction lies between pH 6.9 and pH 7.3. Each 100 units has 0.75 to 1.25 mg. of protamine sulphate and 0.2 mg. of zinc.

Should be stocked in cool, temperature not exceeding 20°: this maintains potency for about 2 years. The label should have the date of manufacture.

Dose is as determined by the physician given by injection. Usually 40 units per ml. strength is dispensed.

Pharmacology [and Therapeutics]

Insulin is the internal secretion of the β -cells of the islets of Langerhans necessary for the metabolism of carbohydrate. The exact mode of action of insulin is unknown. This secretion, as prepared for therapeutic purpose, introduced by hypodermic injection in a diabetic, in adequate dose, reaches the blood and is carried to the muscles and other organs to enable them to utilize glucose, so that the latter is oxidised in the system into CO_2 and H_2O and the balance is stored in the muscles and in the liver as glycogen.

Insulin is rapidly destroyed by alkali, but it is more stable in weak acid solution. It is also destroyed by pepsin and trypsin and so it cannot be given orally. It is therapeutically very efficient, another example of highly successful replacement therapy.

If the natural secretion of insulin is insufficient as in *diabetes mellitus*, glucose is not adequately metabolised and as a result the general nutrition fails and blood sugar persistently rises above normal causing hyperglycæmia and glycosuria : fat is incompletely metabolised and intermediate products of combustion as β -oxybutyric acid, aceto-acetic acid and acetone appear, easily detected in the urine. This condition is called *diabetic ketosis* and if these products cannot be rapidly oxidised, coma sets in and death follows. For the treatment of this condition, insulin is the specific.

The internal secretions of the anterior pituitary and the suprarenals raise the blood sugar and in a normal person this is adjusted by insulin. What share any probable loss of balance between them may have in production of diabetes mellitus is as yet uncertain.

In treating a diabetic, preliminary starvation of the patient is unnecessary especially if any complication is present. About 70 g. of fat in the diet is preferred as in these cases, blood cholesterol is already high ; protein, about 1 to 1.5 g./kg. body weight is usually sufficient and the rest is obtained from carbohydrate. The total requirement is estimated in consideration of age, body-weight and the nature of the occupation. For an adult doing mainly sedantary work, 25 to 35 calories/kg. body-weight may do and one doing more laborious work require more calories. It is convenient to divide the total ration into 2 small and 2 big meals. A nearly full calorific diet containing carbohydrate, protein and fat in the above proportion may be immediately given along with the necessary dose of insulin, twice daily $\frac{1}{2}$ hour before the two principal meals. The maximum insulin effect is produced in an hour or two and this lasts for 5 to 8 hours (a good effect for 3 to 5 hours). But as this passes off, the blood sugar tends to go up again.

In a healthy person, insulin is constantly produced in the system throughout the day with periodic greater supply following carbohydrate ingestion. Such a constant and adjusted supply is not possible with insulin supplied parenterally from outside.

In the therapeutic administration in diabetes mellitus, in some cases at least, the usual soluble insulin (C.I.), even in 2 or 3 divided doses, causes sharp alterations in blood sugar level so that the patient may suffer from marked hypoglycæmia soon after the injection and glycosuria and ketosis during the interval. The former is particularly dangerous at night.

INSOLUBLE INSULIN.—Attempts have been made to prepare insoluble insulin which has a slower but fairly constant rate of

absorption causing a more steady insulin level in the blood. Protamine insulin was first prepared (Hagedorn, 1936). This is rather unstable. This was improved to a combination of *crystalline insulin with protamine and zinc* (P.Z.I.): Scott and Fisher, 1936, forming a colloidal emulsion which was found to have the desired effect. The maximum effect after a subcutaneous injection is produced in ten hours or more after and may continue for even 48 hours (maximal effect for 12 to 24 hours), largely depending on the dose. There is no rapid fluctuation of blood sugar level.

The preparation is buffered by adding sodium phosphate buffer to about pH 7.1 (near to body fluid). If on standing, the suspended matter sinks at the bottom of the vial, it is rediffused by gentle shaking. Further the preparation is comparatively unstable and should not be used after certain specified time.

Globin insulin (GI) has insulin 80 units, globin a protein derived from red blood cells, 3.04 mg. and zinc chloride 0.24 mg.: makes a clear solution, has an effect intermediate between standard insulin and zinc protamine insulin (maximal effect, lasts for 6 to 8 hours).

In fixing up the *dose* of insulin, the extent of the carbohydrate metabolism deficiency is first made out by glucose tolerance test. Insulin is given one unit for every 3 grammes of carbohydrate to be metabolised, hypodermically before principal meals. After the initial blood sugar estimation, subsequent operations may as well be done in consideration of urine glucose: one unit is given for every 1.5 to 2 g. of glucose. The urine should be examined for sugar 4 times daily (a) the first urine of the morning including night's collection: (b) at 11 A.M. (after breakfast): (c) at 4 P.M. (after mid-day meal) and (d) at 9 P.M. (after night meal) and occasionally, the blood sugar also. If much sugar is still present the dose of insulin is gradually increased till the blood sugar is nearly normal, (0.1%) and not more than a faint trace of sugar is present in the urine. At certain times, the patient may be unusually resistant requiring larger doses of insulin (*insulin wasters*) but often this is a temporary phase.

To have proper therapeutic effect, in a *severe* case of diabetes, it is preferable to administer the ordinary soluble insulin hydrochloride in proportion of 2 to 1 with zinc protamine insulin in the morning about 20 minutes before breakfast which will metabolise glucose absorbed during the day and protamine zinc insulin continuing its action at night to have the slow and steady action on the night meal. A second dose with night meal may be given if necessary. In other cases $\frac{3}{4}$ th of the calculated daily dose of insulin is administered as protamine zinc insulin 1 to 1½ hours before breakfast and the remaining $\frac{1}{4}$ th as soluble insulin before the night meal, 1 to 2 hours before retiring. In *milder* cases, one injection of zinc protamine insulin before breakfast may be sufficient. The start may be made

with 10 to 15 units and 4 to 10 units may be added till the fasting blood sugar level is between 80 to 100 mg.%. If the morning sample is sugar-free but the day samples show sugar, a supplementary dose of crystalline insulin is also given along with zinc protamine insulin. With combined treatment consisting of soluble and insoluble insulin, the maximum effect of an injection appears 3 to 4 hours after and lasts for 18 hours and even longer. As the individual response varies, a cut-and-dry scheme may not suit all patients.

The result of summation of several doses (*cumulative action*) must be watched for when insoluble insulin is given.

Insoluble insulin has the advantage of more prolonged and uniform action so that both hyperglycæmia and ketosis disappear and in many cases one injection daily may have the above desired effect. But in some cases late and insidious hyperglycæmia may develop and there may be fitful absorption causing uncertain effects. In other cases again, the effect takes several days to appear.

Insulin should be used at first under strict supervision and the ambulant patients are not treated until the effect is observed under continuous control and the proper dose is fixed up.

Whichever way this is done, with suitable doses of insulin, the carbohydrate metabolism (consequently the metabolism as a whole), is maintained at its normal level. The general condition including the working capacity of the person is made nearly normal. But the disadvantage is that insulin injections have often to be continued nearly life long.

The sites of injection sometimes show atrophy of the subcutaneous fat and even of the muscle tissue and care must be taken not to use the same place too frequently. In exceptional cases, there may be local and constitutional reactions also.

Some of the β -cells of the pancreas not completely destroyed, may now regenerate, carbohydrate tolerance improve and it may be possible to do with a smaller dose and afterwards even without insulin. This more commonly happens in juvenile diabetes. But, other cases eventually go down-hill and require progressively increasing dose of insulin life long.

COMPLICATIONS.—More food and also bigger doses of insulin are necessary when diabetes is complicated by tuberculosis, acute infection or grave septic conditions. The food must yield 3500 to 4000 calories and the dose of insulin be adequate. In a septic condition, insulin is less active and so bigger doses are necessary.

Simultaneous administration of alkalies is not usually necessary. The base exists in the extra cellular fluid combined with organic acids (ketones). Insulin oxidising the acids, liberates the alkalies and additional administration of alkalies may cause dangerous alkalosis.

Insulin is the specific for **diabetic coma**. If this is impending, 50 grms. of glucose orally and 100 units of soluble insulin hypodermically are given at once. The blood is taken 4 hours after for

sugar estimation : if this is still near to 300 mg.%, another 50 units should be given. If it is not possible to examine the blood, the urine is examined 6 hours after. If acetone is still present, more glucose and insulin are given till the acetone bodies are completely burnt off with intensive carbohydrate combustion. If the patient is comatose, both insulin and glucose are given intravenously. When such big doses of insulin are given, sufficient glucose is also necessary to prevent hypoglycæmia. Therefore unless the blood sugar is very high, so much of sugared food must be given with insulin as will leave a surplus, the urine always containing some glucose. The associated conditions as dehydration and circulatory collapse are to be guarded against. When acetone has disappeared and only hyperglycæmia remains, the condition is to be treated as one of uncomplicated diabetes.

Insulin has also been given in other conditions of **malnutrition** without diabetes mellitus. A comparatively smaller dose is given. Often the appetite improves and the patient can take a larger quantity of food with steady rise of body-weight. In an **acute infection** also, glucose and insulin (but in much smaller doses) are indicated.

An overdose of insulin causes *hypoglycæmia*. The symptoms start shortly or a few hours after the injection of insulin. These usually vary according to blood sugar level. If this level is about 0.07% the symptoms are hunger, fatigue and weakness, nervousness and a sort of inward trembling ; when lowered further, loss of emotional control and inco-ordination of the movement also aphasia, mental confusion, delirium, violence and automatic action (as boarding a train with no recollection of it afterwards) ; vaso-motor disturbances as pallor or flushing, dilatation of the pupils, sensation of heat or chilliness, rapid pulse and profuse perspiration. Blood pressure may be raised (compensatory secretion of adrenaline).

At a level from 0.045' to 0.03% coma sets in with hypotonia, loss of deep reflexes, low body temperature, convulsion and rarely death. Deafness, difficulty of articulation and transient hemiparesis have also been reported.

The pulse is usually rapid and regular, occasionally paroxysmal fibrillation is observed. During hypoglycæmia, angina pectoris and cardiac infarction are apt to occur if the coronary arteries are sclerosed.

To what extent the blood sugar must be lowered to cause symptoms is not constant. It varies markedly in different individuals. If the blood sugar is very high as 0.46%, rapid lowering to 0.15% may cause insulin shock (Mosenthal and Ashe). Hypoglycæmia is relieved by glucose orally in big doses flavoured with orange juice and adrenaline hydrochloride solution hypodermically.

Symptoms with *insoluble insulin* are less marked and may be vague such as lassitude, feeling of fatigue, unsteadiness, headache and sometimes drowsiness. Injection of adrenaline only is of no marked value : plenty of glucose is however essential.

Insulin coma is therapeutically induced for the treatment of **schizophrenia**. A dose of 25 units or more of soluble insulin is given intravenously and coma resulting is allowed to continue for several hours being interrupted when required by intravenous injection of glucose. This is safe and no fatality happens on account of hypoglycæmia.

SUMMARY.—*Insulin*, soluble, partly soluble (globin insulin) or/and insoluble (protamine zinc insulin), is used for the treatment of **diabetes mellitus** in all its stages and especially in ketosis. *Diet*, an adequate dose of insulin (in the normal state and in complications especially during an infective disease or grave sepsis), signs of over action (*hypoglycæmia*) and the *general progress* during treatment require careful consideration.

INSULIN SUBSTITUTES (Not official)

SYNTHALIN, SYNTHALIN B.—Alkyl-guanidine derivatives are given orally 2 tablets containing 10 mg. to start with, after food twice or thrice daily and may be increased. These are toxic to the liver and are now seldom used.

TRYPSOGEN and PANCREPATIN.—These are tablets made of pancreas : 4 to 6 tablets are given orally. None of these are as dependable as insulin and are the relics of pre-insulin days and disappearing.

ALLOXAN an oxidation product of uric acid has the property of destroying the beta cells of the pancreas causing diabetes in the experimented animal. This is not yet of any therapeutic use : was tried in carcinoma of the islets but the results were not sufficiently satisfactory.

LIVER AND STOMACH

These are mainly used for the treatment of macrocytic anæmia.

RED BLOOD CELL FORMATION

The *red blood cells* and their precursors are formed in the red bone-marrow. In an adult, the latter is present only in a small patch at the upper ends of the diaphyses of long bones and also in the vertebræ, sternum, ribs and bones of the skull and the pelvis. The nutrient artery of these bones breaks into a net-work of intercommunicating sinusoids, lined by a thin layer of epithelium. Many of these sinusoids under normal condition are completely collapsed without any active circulation. These are the sites of the red blood cell formation.

In a normal state of health, the destruction and regeneration of the red blood cells are going on side by side (the average life of each being about 4 weeks), maintaining the total of about 5 millions with hæmoglobin of 90 to 95%. For regenerating the blood cells as required for normal replacement, only a few of the sinusoids acts but in a case of greater blood loss requiring more rapid replenishment, a larger number gets active. Their endothelial lining becomes swollen and the cells divide repeatedly producing various immature cells which fill the sinusoids completely. The cells are with reticulated nuclei, sticky and bigger than the normal red cells. In successive stages of development, they gradually become smaller in size, lose the nucleus, collect hæmoglobin and become the normal red cells. The sinusoids now open out and these cells enter into the general circulation.

In anæmia, the red blood cells are fewer in number. The total hæmoglobin content is also less than normal. But in some cases when the size of the red cells are bigger than normal, the cell-hæmoglobin ratio (colour index) is above normal. In others, the cells are either normal or smaller and the hæmoglobin ratio is either 1 or less than 1. The various types of anæmia are grouped accordingly. These are—

- (i) *Macrocytic, Hyperchromic* (cell diameter and hæmoglobin increased).
- (ii) *Normocytic, Normochromic* (both are normal).
- (iii) *Microcytic, Hypochromic* (both cell-diameter and hæmoglobin are less than normal). Of these the first and the last are clinically more important.

For the formation of new red cells, in addition to *protein* and *salts*, a *hormone* is necessary for the transformation of the reticuloendothelial cells of the bone marrow to normal red blood cells and for the hæmoglobin, a ready supply of *iron* is essential. So for therapeutic purposes, these two types of anæmia are treated differently.

Castle found that the mucous membrane of the stomach secretes an enzyme-like thermolabile (destroyed by heating to 70° C) substance, **intrinsic factor** which acting on protein or such allied substances as autolysed yeast or rice polishings called **extrinsic factor**, forms the hormone necessary for the red cell maturation in the bone-marrow. Although the extrinsic factor is present in substances rich in vitamin B complex, this is no part of it.

This hormone is absorbed from the intestine, stored in the liver and to a less extent in the kidneys which has a threshold during excretion. This is carried to the bone marrow when required. In some cases (a) the hormone is not produced (*intrinsic factor* deficient as in primary Addisonian or pernicious anæmia); (b) *extrinsic factor* deficient, (in tropical macrocytic anæmia); (c) in others, it is *not absorbed* (as in various gastrointestinal disorders) and (d) in others again, it is *not stored* (hepatic disorder): consequently, the red cells do not mature. The immature cells, as they enter the peripheral circulation, are largely destroyed by the phagocytic cells of the spleen causing severe anæmia. On account of the presence of a large number of immature bigger red cells in the blood (which contain a proportionately larger quantity of hæmoglobin also), this is called *macrocytic, hyperchromic anæmia*.

The hæmopoietic hormone has been isolated for therapeutic purposes both from the liver and the stomach.

Haematics

HÆMATICS are drugs that form either the normal red blood cells (*gastro-hepatic hormone*) or hæmoglobin (*mainly iron*) in adequate proportion so that in near about five million red cells, 95 to 100% hæmoglobin is stored and maintained.

A DRUGS USED AS HÆMATIC FOR THE TREATMENT OF MACROCYTIC HYPERCHROMIC ANÆMIAS.

These are obtained mainly from the *liver* and to a less extent from the *stomach mucous membrane*.

Folic acid (p. 296) and *vitamin B₁₂* (p. 298) are already taken up.

LIVER

OFFICIAL PREPARATION.—**Extractum Hepatis Liquidum** (*Ext. Hepat. Liq.*), See p. 40. This should be kept in a well closed container in a cool place and used as soon as possible after the manufacture. The label should state the equivalent of fresh liver. DOSE, 1 fluid ounce or 30 ml. This is the equivalent of 8 oz. or 240 grammes of fresh liver.

EXTRACTUM HEPATIS SICCCUM (Not official).—This is the dry extract or a selected fraction of the above and is a light brown, very hygroscopic powder with a faintly meat-like smell and taste.

DOSE, the quantity equivalent to about $\frac{1}{2}$ lb or 225 grammes of fresh liver.

Pharmacology [and Therapeutics]

In August 1926. Minot and Murphy reported that by giving a diet rich in liver, they were able to cure some cases of macrocytic (pernicious) anæmia which were so long nearly incurable. The result was corroborated by other workers and it was found that about half a pound of raw or partially cooked liver of an ox taken daily could supply the necessary hæmopoietic principle lacking in these cases. But many would not take sufficiently long such a big quantity of a rather unpalatable stuff, others got diarrhoea and in others again, vomiting that was already present, got aggravated.

1. It was found that a water-soluble, non-protein and iron-free product in the liver was the **hæmopoietic principle**. This was isolated and made into liquid and powdered liver extract which marked the next stage of improvement. (Cohn and Minot, 1927). This is thermostable at 100° and not destroyed by gastric ferments.

This is called Cohn's G fraction. It has been found possible to concentrate in 12 grammes, the G fraction of 400 grammes of the raw liver, as effective for blood formation as 250 gm. of the whole liver.

Later, Gæsslen (1930) and others prepared a highly concentrated liquid extract suitable for *intramuscular injection*. The efficiency of a preparation is estimated in consideration of the reticulocytic response caused in a case of pernicious anæmia. A good preparation by intramuscular injection, produces the effect of at least 20 to 30 times of liver taken orally.

The advantages of the intramuscular injection are, (i) in a small volume, a much bigger dose of the antianæmic factor may be given; (ii) the disadvantages of bowel complications and uncertain absorption are obviated; (iii) if a big dose as 5 c.c. is given, a depot is formed at the site of injection with slow and sustained absorption therefrom and consequently the interval of injection may be increased. (iv) A definite amount of the active substance is thus administered with lesser possibilities of lapse or error. (v) Injection is nearly painless.

The injection is now the accepted method of intensive liver therapy. Dose is 10 units followed by 5 units daily till good reticulocytosis, afterwards 10 units weekly. There is no special advantage in giving these preparations intravenously.

Recently, even more purified extracts have been prepared (Dakin and West, 1935), *anahæmin*, which with 80 mg. produced maximum reticulocytic response. But although this is the ideal preparation for true pernicious anæmia, this is

less effective in tropical macrocytic anæmia than the cruder or "whole liver" products. This is a water-soluble non-protein containing carbon, hydrogen, oxygen and nitrogen : 4 c.c. initially followed by 2 c.c. weekly suffice. But as the hæmo-poietic principle consists of several factors, a highly purified unitary product has a limited field of utility.

The normal gastric juice incubated with the G fraction of the liver has been found to be more effective orally in smaller doses (Helmer, Fouts and Zerfas, 1933).

The cruder product before the final separation of G fraction by 95% alcohol and after removal of proteins, carbohydrates, lipoids, tyrosine, tryptophane, arginine, cystine, iron, sulphur and phosphorus, is mostly polypeptides containing antianæmic principle, Cohn's fraction D and extrinsic factor as vitamin B complex, Castle's factor and folic acid of liver. This is water soluble and is more effective in *tropical macrocytic anæmia*, has a prophylactic and curative value for *toxic action of arsenic* and is useful in *agranulocytosis*.

The whole liver contains in addition, iron, vitamin C, a trace of copper and also probably a "secondary anæmia" fraction (Whipple). This has a wider field of usefulness especially in *sprue*, *tropical macrocytic* and in *pregnancy anæmias*.

Thus, it is likely that the *anti-anæmic factors* are of three types : of pernicious anæmia, tropical macrocytic anæmia and of secondary anæmia.

2. Liver has a **neuropoietic factor** also. This is particularly useful to prevent and cure degenerative changes that may take place in the spinal nerve tissue in pernicious anæmia.

[By combination of the intramuscular injection of a purified and standardised preparation 1 to 5 c.c. daily or every other day, afterwards once a week in 5 c.c. doses or less and later on, oral administration of liver in various forms where possible, many cases of *pernicious anæmia*, hitherto incurable, are now cured]. The pernicious anæmia factor has recently been isolated and is called vitamin B₁₂ (p. 298) and this should be one of choice in true pernicious anæmia. But in *sprue*, *tropical macrocytic anæmia* and in *pregnancy anæmia*, the whole liver extract may be with folic acid, (p. 296) is more suitable. *Allergic reactions* as headache, fever, urticaria and in very rare cases, shock and collapse may occasionally occur.

As the disease is in many cases a **kind of deficiency**, the administration, oral or periodically intramuscular, should be kept up fairly long even during the remission stage.

The evidences of improvement are (i) degree of *reticulocytosis* which is more marked if anæmia is severe when the treatment was started. (ii) *Red blood corpuscles* increase in number near to 5,000,000, of normal size and appearance. (iii) *Clinical improvement* is shown by better complexion of the skin and of the mucous membrane, gain in strength, improvement in

appetite and digestion (although achlorhydria may continue) and improvement of the neurological signs also.

SUMMARY.—Liver has a hæmopoietic hormone highly successful in the treatment of all types of **macrocytic anæmias**: *purified extract* for pernicious and *whole liver extract* for other types of anæmias: given orally or parenterally.

COMMERCIAL PREPARATIONS

STOMACH TISSUE DESICCATED (of pig) and a special preparation of it, *Ventriculin* 20 gm. or *Hæmo-ventriculex* $\frac{1}{2}$ to 1 oz., is given orally daily. In a favourable case, there is good response in a week.

The cells of the gastric mucosa have the enzyme which acts on the chopped muscles on the gastric walls and in this way produces the antianæmic factor.

Liver Extract (Lilly, 1, 2 and 15 units per c.c.) and (P.D. 1, 2, 5, 10, 15 units per c.c.): *Campolon*, *Campanæm Hepostab forte*, *Liver extract crude*, *Heparglandol B*, *Hepol*, *Inj. Liver extract B.W.* and *Whole Liver Extract T.C.F.* in 2 c.c. ampoules are whole liver preparations. *Anahæmin*, *Neo-hepatex*, *Hepatex T.*, *Livadex* and *Livarex* (these cause rapid reticulocytosis 1 to 3 c.c.) are given daily intramuscularly for intensive liver therapy. *Livadex* oral and *Hepatrat drinkable* in 10 c.c. ampoules representing 100 gm. of fresh liver given orally. *Extralín* (G fraction incubated in human gastric juice), 4 to 12 pulvules daily: *Lextron* (liver-stomach concentrate with iron and vitamin B), 4 to 8 pulvules daily. *Powdered Extract* contains in each tube antianæmic fraction of 100 gm. raw liver. (P.D. and Lilly): given orally.

Proteolysed liver, *Hepamine*, *Prohepex* in powder, prepared by digestive process so as to destroy the nauseating taste fully keeping the hæmopoietic factor: these have in addition the protein food factor.

DOSE, 15 to 30 g. (4 to 8 heaped up teaspoonfuls) given in soup or in warm water: maintenance dose, 4 to 8 g. (1 to 2 tea-spoonful). These are specially suitable in pregnancy, sprue and nutritional anæmias.

B-complex Liver extract, *Siotrat*, liver extract with vitamin B-complex and *Folvite* with liver extract (contains folic acid also) in 10 c.c. rubber-capped vials. Dose, 2 c.c. intramuscularly daily or weekly.

B. DRUGS USED AS HÆMATIC FOR THE TREATMENT OF HYPOCHROMIC MICROCYTIC ANÆMIAS.

The main constituent of hæmoglobin is *iron*; this is consequently essential for the treatment of this type of anæmia. In addition, probably a trace of *copper*, *vitamin C* and *thyroxine* are also necessary.

FERRUM, IRON, *Lauha*

1. FERRUM, (*Ferr.*), Iron free from oxide.

This is fine, bright iron wire, 0.1 millimetre in diameter.

OFFICIAL PREPARATIONS.—**Syrupus Ferri Phosphatis Compositus** (*Syr. Ferr. Phosph. Co.*), See p. 55. *Parish's food*, *Chemical food* (0.9% w/v of anhydrous Ferrous Phosphate and 1.4% w/v of tricalcium phosphate). **DOSE**, 30 to 120 minims or 2 to 8 ml.

2. FERRI CARBONAS SACCHARATUS (*Ferr. Carb. Sacch.*).

Prepared by the interaction of Ferrous sulphate 1000 g., liquid glucose 307 g., sodium carbonate 1078 g. and distilled water q.s.

Washed precipitate obtained is mixed with liquid glucose, dried at 100° and the product powdered. Sugar forms a coating and stops oxidation of the iron.

Saccharated iron carbonate is a greenish brown powder slightly soluble in water, containing not less than 50% of ferrous carbonate, FeCO_3 .
Dose, 10 to 30 grains or 0.6 to 2 gramme.

3. FERRI SULPHAS (*Ferr. Sulph.*), Ferrous Sulphate, (*Hirakas*), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$.

Oblique, pale greenish rhombic prisms or pale bluish green powder prepared by the action of dilute sulphuric acid on iron: contains 98 to 105% of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$. Soluble at 15.5° in $1\frac{1}{2}$ of water, insoluble in alcohol 90%.

Dose, 3 to 5 grains or 0.2 to 0.3 gramme.

4. FERRI SULPHAS EXSICCATUS (*Ferr. Sulph. Exsic.*), FeSO_4 .

A greenish white, hygroscopic powder, made by drying ferrous sulphate at 40°C . till it contains not less than 77% of FeSO_4 and 3 grs. (0.2 g.) of this contains 1 gr. (0.06 g.) of iron.

Dose, 1 to 3 grains or 60 to 200 mg.

Pilula Ferri Carbonatis (*Pil. Ferr. Carb.*), *Blaud's Pill*.—See p. 52.

The pill contains ferrous carbonate which is formed by interactions between ferrous sulphate and sodium carbonate.

Dose, 5 to 30 grains or 0.3 to 2 grammes.

SCALE PREPARATIONS

These are not stable chemical compounds and all of them contain ferric hydrate. These are at first prepared in solution and then dried to be made into scales and are therefore called "Scale preparations". Only one of these is official.

5. FERRI ET AMMONII CITRAS (*Ferr. et Ammon. Cit.*).

Iron and ammonium citrate may be prepared by saturating a warm aqueous solution of citric acid with freshly precipitated ferric hydroxide, adding a slight excess of a solution of ammonia, evaporating and drying on glass plates at a temperature not exceeding 40° .

Dark red thin transparent scales, deliquescent in moist air, soluble in 0.5 part of water; it contains in 45 grains (3 g.) about 9 grains (0.6 g.) of iron.

Dose, 15 to 45 grains or 1 to 3 grammes.

FERRI ET AMMONII CITRAS VIRIDIS B.P.C. is prepared in the same way but a larger proportion of citric acid is used and sufficient ammonia to cause a green solution: this is evaporated and dried.

6. LIQUOR FERRI PERCHLORIDI (*Liq. Ferr. Perchlor.*), Solution of Ferric Chloride.

An aqueous solution containing 15% w/v of FeCl_3 , prepared by the action of hydrochloric acid dilute on iron. An orange yellow fluid is formed, acid in reaction.

It contains in 15 minims, about $2\frac{1}{2}$ grains of ferric chloride (about 4.5 grain of iron).

Dose, 5 to 15 minims or 0.3 to 1 ml.

INCOMPATIBLES.—All vegetable preparations containing tannic and gallic acids: alkalies and their hydroxides and carbonates and magnesia give green precipitate with the ferrous and brown with ferric salts. *Ferri et Ammon. Cit.* can be dispensed with alkalies. The inky mixture that tannin forms with iron may be clarified by adding a few drops of dilute phosphoric acid. But after some days, a precipitate of phosphate of iron forms.

Pharmacology [and Therapeutics]

Iron is the essential constituent of **hæmoglobin** and of almost all forms of protoplasm. Iron is an important catalytic agent for the **normal cell oxidation**.

A bio-catalytic property of certain iron compounds have been described. By losing oxygen, a trivalent iron becomes divalent which again under the medium of oxidation, can be reconverted into a trivalent compound without greatly altering the medium in which this catalysis occurs. Iron appears to assist and control respiration and other chemical processes of the cells which function appears to be indispensable for tissue life and this is as important as its participation in cell formation and synthesis of blood pigment (Vannotti and Delachaux, 1948).

In health a certain number of red blood corpuscles is broken down every day and the hæmoglobin is liberated. The pigment is changed to bilirubin and excreted in the urine and fæces but iron is mostly restored to the body: so iron is not much lost and the small amount that is taken daily in the food is sufficient to compensate. This is about 5 to 10 mg. daily.

The amount of iron in different articles of food varies: in the liver 0.015%, spinach and several other green vegetables 0.005%, meat 0.002 to 0.005%, bread 0.002%, potatoes 0.0012% and in cow's milk, a faint trace.

In many *diseased conditions* of pathological blood loss, where the hæmoglobin of blood is deficient, as in many cases of hypochromic microcytic anæmia, more iron is necessary than is obtainable from ordinary food. In such cases, therapeutic administration of iron has been found effective in making good the deficiency, although the process is slow.

But in those types of anæmia where the deficiency is not so much of hæmoglobin as of the cellular elements of the blood, as in pernicious anæmia and various types of leukæmia, an iron preparation is not primarily necessary.

APPLIED EXTERNALLY, the iron salts produce *local action* in proportion to their dissociability and the presence of the acid-radicle. Ferric salts have more active local action than ferrous and organic iron salts. Therefore, locally, the easily dissociable solution of ferric salt, the perchloride, is the most powerful **astringent** of all. The next is the sulphate. The least active are the scale preparations. These have no action on the unbroken skin but on a raw surface or on the mucous membranes, the more powerful ones coagulate protein. The secretion is reduced and the coagulated albumin compresses and plugs the arterioles. Therefore these are **astringent** and **hæmostatic**²⁶⁷.

(267) B

Ferr. Chlor. gr. 10

Paraff. Moll. Flav. oz. 1

Ung. For piles.

In a concentrated solution, the perchloride is **irritant** and even **corrosive**, for it contains a certain amount of free hydrochloric acid. But, unlike mercury, the iron-ion itself is not definitely poisonous to the living cells. There is no action on the intact skin.

[Therefore these acid salts are sometimes prescribed for their local action as paint²⁶⁸, gargle²⁶⁹ or wash for various inflammatory conditions in the mouth, throat and less commonly in the nose and rectum²⁷⁰.]

TAKEN INTERNALLY by the mouth, these have an **astringent metallic taste** and blacken the teeth, iron combining either with tannin contents of the food or sulphides present in tartar or in caries of the teeth. In the stomach, the same **astringent** effect is produced [and so these preparations are given after a meal to be well diluted with the food stuff.] In big doses and in a concentrated form, the ferric (and to a less extent ferrous) salts are gastro-intestinal irritants and may upset digestion, cause headache, nausea, vomiting and even diarrhœa.

The astringent effect is also continued into the intestine, often resulting in **constipation**.

For SYSTEMIC ACTION, iron salts are frequently used.

The modern conceptions of the method of *iron absorption*, increase in *hæmoglobin* and *serum iron concentration* have been considerably advanced by the use of radio-active iron.

ABSORPTION.—Iron is absorbed from the stomach and small intestine (mainly from the upper part) and also slightly from the colon. By observing the behaviour of radio-active iron, it appears that this absorption takes 4 to 8 hours.

The free acid in gastric juice dissolves and ionizes iron. This is precipitated in fine division in the small intestine and is quickly absorbed. So the substances that retard solution or form insoluble compounds with iron, also retard absorption of iron. Ferrous salts are better absorbed than the ferric salts. A healthy person utilizes 1·5 of ferric iron against 10 of ferrous iron and one with iron-deficiency anæmia, this is 2 against 15 (Witts, 1936 and Moore, 1944).

The absorption of iron is in proportion to the bodily need. When the available iron including the iron reserve is very much exhausted by repeated bleeding, the dietary iron absorption is increased from a normal of 7% to 33% (Hynes, 1949).

Often there is no definite correlation between the amount of iron present in the alimentary canal and the blood serum level

| | |
|-------------------------------|-------------------------------|
| (268) B | Glycer. min. 240 |
| Liq. Hydrarg. Perchlor. | Aq. ad. fl. oz. 3 (Cohens |
| Liq. Ferr. Perchlor. | and Githens). |
| aa. min. 120 | A gargle for pharyngitis. |
| Glycer. ad. fl. oz. 1 | (270) B |
| A throat paint. | Liq. Ferr. Perchlor. min. 60 |
| (269) B | Aq. Dest. ad. fl. oz. 8 |
| Pot. Chloras gr. 60 | A rectal injection for thread |
| Liq. Ferr. Perchlor. min. 120 | worms. |

and for this discrepancy, the presence of some "iron-acceptor-mechanism" in the gastric and intestinal mucus membranes has been speculated. After oral administration of iron in a normal person, this acceptor mechanism may be saturated in 1 to 2 hours but desaturation takes several days. But in *iron-deficiency anaemia*, desaturation is more rapid, so that iron from the iron acceptor is more readily transferred to the plasma and more iron from the gastro-intestinal lumen passes into the iron acceptor (Hahn, 1943).

Granick (1947) explained this in another way. He found that the duodenal mucosa of a normal guinea-pig has only a trace of ferritin. By feeding with iron, in 7 hours this was found in the mucosa of the whole gastro-intestinal tract and it took, 3 to 6 days to reach the previous normal level: this thus resembles saturation-desaturation phenomena of Hahn. He further suggested that the saturated mucosal cells are in a saturation-equilibrium between the pre-existing ferrous iron and ferric iron of ferritin now introduced. When ferric iron is decreased and the cells are no longer saturated with ferrous iron and more iron will be absorbed. Thus in chronic hæmorrhagic anaemia, there is a fall in the serum iron level and ferrous iron from the mucosal cells enters into the blood stream: the mucosal cells in their turn absorb more iron from the alimentary canal.

IRON TRANSPORT.—In a normal healthy person, a single dose of 10 g. of iron and ammonium citrate could raise the serum iron level from 100 to 360 $\mu\text{g.}$ per 100 ml. in $4\frac{1}{2}$ hours: this would return to original level in 24 hours. It appears that plasma transmits this extra iron from the site of absorption either to the bone marrow for utilization or to the iron store and the original level in plasma is reached in this way.

Laurell (1947) found that the total plasma iron is about 0.1% of the total iron store in the body and is about 4 mg. and since about 25 mg. of iron is required daily for hæmoglobin synthesis, the balance of iron must be obtained from supply from outside, red blood cells breakdown and from the store and transported to the bone marrow. He found further, 315 $\mu\text{g.}$ was the maximum saturation limit for 100 ml. of plasma but the normal plasma level is $\frac{1}{3}$ of this. In chronic hæmolytic anaemia, plasma level of iron being lowered, the saturation limit is raised and this also happens in the later part of pregnancy.

Surgenor (1949) found that plasma protein that combines with iron is β_1 globulin and this is about 3% of total plasma protein and Ruth and Finch (1949) found that 1 mg. of this β_1 -globulin combines with 1.25 $\mu\text{g.}$ of iron and on account of high O_2 tension in the blood, this is probably ferric iron (Granick). Iron is stored in the liver, spleen, kidneys and bone marrow mainly as ferritin (Granick and Hahn, 1944).

DISTRIBUTION.—(i) Iron in circulation as blood hæmoglobin is 57% : (ii) available iron reserve in the liver, spleen, bone-

marrow and from else where is about 20% and (iii) *non-available* iron reserve as myohæmoglobin and parenchyma iron is 23% (Hahn, 1937). The available iron reserve is 850 mg. and in a healthy person, loss of $\frac{1}{3}$ of hæmoglobin in circulation can be made good without any iron intake but after prolonged repeated bleeding, this reserve falls.

UTILISATION.—For hæmoglobin formation, iron liberated from hæmolysis is first utilised and next, iron therapeutically administered: these are called the “labile pool” (Greenberg and Wintrobe, 1946): when these are not adequate, the stored reserve is called upon.

EXCRETION.—This is slight: in the *urine*, 0.5 mg. daily and in the *bile*, 0.6 to 0.8 mg. (a part of this is reabsorbed again): total daily loss in a man is about 1 mg. Menstrual loss in a woman is 10 to 40 mg. monthly and approximately 1 mg. daily and the total loss in her is 2 mg. daily. So in a healthy person to balance this, a man should take a minimum of 5 mg. and a woman and a growing child, 15 mg.: it is presumed that about 10 to 12% of this is only utilised (Hahn, 1948).

IRON DEFICIENCY ANÆMIA.—The normal blood (plasma and hæmoglobin) contains 50 mg. of iron per 100 ml. It may be remembered that 1 g. of hæmoglobin contains 3.34 mg. of iron and about 25 mg. of iron are required to increase hæmoglobin level by 1%. In a case of severe blood loss, the deficiency can not be made good from dietary iron only and therapeutic administration is necessary. But the process of hæmoglobin formation is slow and the full value is reached in several weeks.

Iron and ammonium citrate is popular as it is soluble, does not readily precipitate protein, is not irritant and not oxidised into a ferric salt in the mixture. It is given in increasing doses, 45 to 90 grains daily to be effective. Bland’s pill (containing ferrous carbonate, 45 grains daily), citrated ferrous chloride (10 grains daily), ferrous sulphate (9 grains daily) and the syrups of iron iodide and iron phosphate (containing ferrous iodide and phosphate $\frac{1}{2}$ oz. daily), are also frequently prescribed but in a much smaller dose. Although only a small quantity of iron is utilised, an abundance of supply is more effective. The addition of a minute quantity of *copper* (3mg.) is also probably necessary for the formation of hæmoglobin.

The inorganic or dissociable preparations are partly changed into *chloride* (ferric and to some extent ferrous) in the stomach which is further changed into *carbonate* in the small intestine. The latter is again changed into *sulphide* by combining with the sulphur compounds present in the intestine and also into *tannate* by combining with tannin contained in the food and passed out with the stool which consequently turns black.

Further (a) in a case of *infection*, the iron-binding capacity of serum decreases and hæmoglobin regeneration is delayed:

in *other cases* (b) diminished absorption from the alimentary canal or (c) diminished utilisation of iron in hæmoglobin synthesis may be the factors responsible for impaired hæmoglobin formation.

In such cases, *parenteral administration* of iron may be more effective than the oral method. In cases refractory to oral administration, 25 mg. of saccharated iron oxide daily intravenously, increased up to 200 mg. daily or twice weekly may cause nearly 100% hæmoglobin formation: in some cases even bigger dose may be necessary. Toxic symptoms may follow if the dose exceeds 300 mg. daily.

AVAILABLE as *Ferrivenin* and *Iviron*, a 5 c.c. ampoule containing 100 mg. of saccharated iron.

[Iron in different forms is frequently prescribed in various types of **hypochromic anæmia** orally after food with great benefit^{271, 279}]. If achlorhydria is also present, dilute hydrochloric acid is necessary along with iron.

It is also of some value in **advanced hyperchromic anæmias** improving on liver-stomach treatment. In these as many new, normal-sized, red blood cells are being formed, the existing stock of iron may fall short of the requirements. More iron must be supplied to maintain the full hæmoglobin level of these cells.

Iron has no direct action on the general metabolism. But by curing anæmia, it often increases the bodily strength and

- (271) \mathcal{B}
 Liq. Ferr. Perchlor. min. 15
 Liq. Arsen. min. 3
 Tinct. Nuc. Vom min. 10
 Glycer. min. 20
 Aq. Chlorof. ad. fl. oz. 1

A blood tonic.

- (272) \mathcal{B}
 Ferr. Sulph. gr. 3
 Mag. Sulph. gr. 30
 Quinin. Sulph. gr. 3
 Acid. Sulph. Dil. min. 10
 Glycer. min. 20
 Aq. Anis. ad. fl. oz. 1

Popular "*Spleen Mixture*".

- (273) \mathcal{B}
 Ferr. Subchlorid. Cit. gr. 3
 Cupr. Cit. gr. $\frac{1}{2}$
 Glycer. min. 30
 Inf. Quass. Rec. ad. fl. oz. 1

A bitter hæmatinic.

- (274) \mathcal{B}
 Ferr. et Quinin. Cit. gr. 15
 Liq. Strych. Hydrochlor.
 min. 3

Sp. Chlorof. min. 15
 Inf. Calumb. Rec. ad. fl. oz. 1
 A tonic during convalescence.

- (275) \mathcal{B}
 Ferr. et Ammon. Cit. gr. 15
 Cupr. Cit. gr. $\frac{1}{2}$
 Liq. Arsen. min. 2
 Aq. Chlorof. ad. fl. oz. 1

Hæmatinic.

- (276) \mathcal{B}
 Ferr. Sulph. gr. 2
 Aloe gr. 1
 Ext. Nuc. Vom. Sicc.
 Ext. Bellad. Sicc. aa. gr. $\frac{1}{2}$
 Trag. and Liq. Glucos. q.s.
 Pil. For anæmia with amenorrhœa.

- (277) \mathcal{B}
 Aloin. gr. 1/10
 Ext. Casc. Sagr. Sicc. gr. $\frac{1}{2}$
 Pil. Ferr. Carb. gr. 3
 Pulv. Tragacanth. Co. gr. $\frac{1}{2}$
 Glucos. Liq. gr. 1 $\frac{1}{2}$ or q.s.
 Pil. For anæmia with constipation.

- (278) \mathcal{B}
 Ferr. Sulph. gr. 1
 Acid. Hypophosph. Dil. m. $\frac{1}{2}$
 Dextros. gr. 15
 Aq. Chlorof. ad. min. 60
 Stable ferrous mixture for a child of 1-2 years.

vigour, improves circulation and also cures amenorrhœa. The tongue if ulcerated now becomes normal and the nails regain their normal size and shape. It is therefore often used as a general tonic.

It is not definitely proved to have any diuretic properties when given by the mouth. [But it is helpful in cases of chronic nephritis²⁸⁰: probably it acts by its hæmatinic properties].

Hydroxide of iron²⁸¹ is a chemical antidote to arsenic poisoning.

SUMMARY.—Iron is necessary for hæmoglobin formation and it takes part in a biocatalytic activity. In *health*, the daily loss of iron is about 1 mg. and in a parous woman 2 mg., this being obtained from food. In *disease* causing **hypochromic anæmia**, therapeutic administration of iron is necessary *orally* as a ferrous iron: in delayed hæmoglobin formation especially in severe anæmia, saccharated iron oxide *intravenously*, commencing with 25 mg. daily is the method of choice.

Non-official Preparations

FERRI PYROPHOSPHAS SOLUBILIS, contains about 10% of iron and may be given subcutaneously in 2 to 4 grains doses.

FERRI ET MAGNESIUM CITRAS.—Red scales freely soluble in water given in 2 to 5 grains doses.

FERRI ET QUININÆ CITRAS, quinine 15% and iron 14%, 5 to 15 grains.

MALT EASTON.—Easton's syrup (See p. 337) with an equal part of malt extract.

DOSE, 60 to 120 minims.

SYRUPUS FERRI IODIDI is 3.75 gr. of ferrous iodide in 60 min. of syrup.

DOSE, 30 to 120 min. or 2 to 8 ml.

Ribothiron (Ferrous Sulph., thiamine and riboflavin); *Ferolet*, *Fersolate* (Ferrous sulph. with Cu. and Mn.); *Hemochromin* (Ferrous sulph. with liver extract or with folic acid); *Plastules Hæmatinic* (Ferrous sulph. and yeast pill, plain, with liver extract or folic acid); *Lirimin* (Ferrous sulph. with liver-yeast and vitamin B complex); *Nutritive capsules* (Ferrous sulph., Ca and vitamin B and D): one t.d. *Ferradol* (Iron and ammon. cit., Mn. and vitamins B and D), one tea-spoonful t.d.

Liafon capsules (Liver desicc. 0.5 g., ferrous sulph. exsic. 0.13 g., ascorbic acid 50 mg. and folic acid 1.67 mg.), one 2-3 times daily.

COBALTOUS CHLORIDE (Not official).—Cobalt is present in vitamin B₁₂ fraction and a hæmatinic property of it has been speculated. It is suggested that cobalt in some complex manner may cause anoxia of epithelial cells of the bone marrow and stimulate erythropoiesis. Cobalt chloride has been given in 20 to 60 mg. daily *orally* for 2 to 11 weeks with some apparent hæmatological improvement. All patients however developed a dusky red colour below the eyelids.

(279) R

Syr. Triplex.

Easton's Syrup

Fellow's Syrup aa. 1

Parish's Syrup 2 (Edin.)

Mix. General tonic.

(280) R

Liq. Ferr. Perchlor. min. 15

Liq. Ammon. Acet. Dil.
min. 120

Acid. Acet. Dil. min. 15

Syr. Aurant. min. 60

Aq. ad. fl. oz. 1

(Basham's Mixture).

For chronic albuminuria with anæmia.

(281) R

Liq. Ferr. Perchlor. fl. oz. 3

Sod. Carb. oz. 1

Aq. fl. oz. 4 (Shake the bottle)

In arsenic poisoning, ½ oz. every 15 minutes.

IX. OTHER HEAVY METALS

A large number of heavy metals are used therapeutically. Some of these are used mainly for *local action* and the others are for *systemic action* also after absorption.

(a) Those used mainly for **local action** are the preparation of—

Lead, Silver, Zinc, Copper, Aluminium, Bismuth, Chromium and Manganese. Mercury and Iron have both local and systemic actions.

(b) Those used mainly for **systemic action** are salts of Iron, Mercury, Antimony, Arsenic and to some extent also Bismuth. Gold has specific systemic action.

Of these, Manganese, Mercury, Bismuth, Arsenic, Antimony and Iron preparations have been already described and the rest are taken up here.

General Actions

The salts of the heavy metals have twofold actions. *Firstly*, applied locally, the **metallic-ion** acts by precipitating albumin. More rapid and complete the dissociation is, greater is the action. The mechanism is not yet fully understood probably it is more an adsorption-complex than a chemical reaction.

The character of the metal itself is an important factor. Thus mercury is highly poisonous which when applied, causes tissue necrosis but lead is much less active and the cells are not destroyed even if the metal is deposited on them. Therefore, the different metals show actions of varying intensity.

Metals cause coagulation of the microbic protein : these are therefore powerful *disinfectants*, destroying all low forms of animal and vegetable lives even in great dilution. Many in addition are direct *protoplasmic poisons*, as copper or mercury causing tissue necrosis.

Precipitation of protein in the superficial layer of the mucous membrane often forms a protective barrier and saves the part underneath from further action of the metal. This is sometimes helpful in stopping bleeding from a superficial blood vessel. Further, the *astringent* action reduces the local vascular congestion and secretions and is therefore often useful in lessening the inflammation, if any present.

Secondly, the **acid-ion** liberated by dissociation of the metal, acts according to the intensity of its acid property and strength of the solution. Therefore more powerful the acid is, and more readily dissociated in greater concentration, severer is the local effect. Lead chloride on dissociation liberates hydrochloric acid and is therefore a more powerful caustic than lead acetate liberating acetic acid. In this case the acid being

more powerful, its action is more manifested and that of the metal is comparatively masked. For the same reason, the inorganic salts cause more powerful local action than the organic ones such as acetates, citrates and tartrates. Further, salts with great affinity for water, have more powerful local action when applied in desiccated form.

ABSORPTION.—The heavy metallic salts are not readily absorbed when applied locally or even taken by the mouth. The only exception is mercury which is readily absorbed. Iron, lead, silver and manganese are absorbed slowly only in minute quantities.

Given intravenously, taking care to avoid embolism of the coagulated albumin, these do not stay in the blood long enough. Although partly stored in the liver, spleen, kidneys and bone marrow, these are mostly *excreted* into the alimentary canal, in the mouth, stomach and in the intestine. Thus these give a metallic taste in the mouth, cause nausea, vomiting, diarrhœa and less commonly (as with lead), constipation. The process of excretion is slow and many repeated smaller doses, absorbed in quantity not sufficient to cause immediate toxic symptoms, lead to *cumulative poisoning*.

A portion of the absorbed amount is also excreted through the kidneys causing irritation which, if mild, results in *diuresis* but if severe, toxic *nephritis*.

On the **CIRCULATION**, the different metals act differently. There is often a certain amount of cardiac depression and fall in the blood pressure. The latter is partly due to vasodilatation of the splanchnic area.

CENTRAL NERVOUS SYSTEM is affected. There may be symptoms of *mental aberration* or the motor areas of the *brain*, the *basal ganglia* and the *spinal cord* are stimulated causing convulsion and different types of spasmodic movements but more often the *peripheral nerves* are paralysed causing polyneuritis (as lead neuritis).

PLUMBUM, LEAD, *Sisaka*

1. PLUMBI MONOXIDUM (*Plumb. Monox.*), Lead Oxide, Litharge, *Mudrasang*,* PbO.

Prepared by roasting molten lead in air; it contains not less than 99% of PbO.

Pale brick-red or yellowish-red heavy scales or powder, insoluble in water and alcohol (90%) but soluble in dilute nitric and acetic acids and in warm solutions of alkaline hydroxides.

* Red oxide of lead, *minim*, was manufactured by the ancient Hindus and was called dull or *Mete Sindura*.

This coloured with an artificial red dye is sold as *Sindura*. This in many causes local irritation and also occasionally lead poisoning. Vermillion or red mercuric sulphide is the proper *Sindura*.

EMPLASTRUM PLUMBI (Not official).—Litharge Plaster, *Diachylon*: lead soap. Lead monoxide 4 g., olive oil 8 g., distilled water 4 ml. or q.s.

2. **PLUMBI ACETAS** (*Plumb. Acet.*), Lead Acetate, Sugar of lead, $\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$.

Obtained by treating lead oxide or carbonate with acetic acid and water, containing between 99·5 to 104·5% of $\text{C}_2\text{H}_3\text{O}_4\text{Pb} \cdot 3\text{H}_2\text{O}$. Small, white crystals or heavy white masses or monoclinic prisms with acetous odour and sweet astringent taste. Soluble at 15·5° in 2·5 of water, freely in glycerin and in 30 of alcohol (90%).

Dose, $\frac{1}{2}$ to 2 grains or 30 to 120 mg.

INCOMPATIBLES.—Alkalies especially lime water, hard water, soluble chlorides, sulphates, mineral acids (except nitric acid) and salts, potassium iodide, tannic acid, opium and albuminous liquids.

OFFICIAL PREPARATIONS.—(i) **Liquor Plumbi Subacetatis Fortis** (*Liq. Plumb. Subacet. Fort.*), *Goulard's extract*.—See p. 50. Contains 19 to 21·5% of total lead. (ii) **Liquor Plumbi Subacetatis Dilutus** (*Liq. Plumb. Subacet. Dil.*), *Goulard's Lotion* or *Goulard's water*.—See p. 50. In the last two preparations, lead acetate is made into subacetate.

Pharmacology [and Therapeutics]

Lead salts are used for their local astringent action on abraded skin and the mucous membrane. Acetate is usually preferred as its action is not too powerful.

APPLIED EXTERNALLY, on a raw surface, the acetate **precipitates albumin** forming a thick coating which protects the part underneath from irritation and promotes healing. Applied on an abraded area²⁸², it directly constricts the small blood vessels and is therefore a **hæmostatic** and powerful astringent. To some extent it relieves pain also. Unlike mercury it is not corrosive. [Subacetate of lead lotion is frequently used on a piece of lint over a bruise or occasionally used as wash for chronic inflammatory conditions in many mucous surfaces as of chronic gonorrhœa, leucorrhœa and of chronic otorrhœa]. It is also applied to weeping eczema²⁸³. Very little, if any, is absorbed through the unbroken skin from a therapeutic application of short duration.

TAKEN INTERNALLY, the same action of protein coagulation takes place. It acts as a local astringent causing constipation and is also a **hæmostatic** [and is occasionally used in obstinate diarrhœa and gastro-intestinal hæmorrhage and formerly lead and opium pill was frequently prescribed for bleeding from the stomach in gastric ulcer and from the intestine in typhoid fever but is now-a-days obsolete]. Such internal administration as a hæmostatic is of no value in bleeding from

(282) B
Liq. Plumb. Subacet.
Fort. min. 120
Sp. Methyl. Indust. fl. oz. 2
Aq. pint. 1
To apply over bruises.

(283) B
Liq. Pic. Carbon. min. 60
Liq. Plumb. Subacet.
Dil. ad. fl. oz. 3
To apply over weeping eczema.

remote organs as the lungs, kidneys or the uterus as the metal never reaches them in a concentration sufficient to have the local effect.

Lead poisoning causes powerful contraction of the unstriated muscles especially of the *intestine* (lead colic) and of the *uterus* (dysmenorrhœa). Lead acetate is sometimes used to cause criminal abortion.

A special colloidal preparation, containing 0.5% of lead, was used intravenously for the treatment of cancer. The results are uncertain and serious toxic symptoms may also follow.

ABSORPTION and ELIMINATION.—Lead is made into an albuminate and is slowly absorbed, more readily than other metallic salts except mercury and is excreted slowly. It is found in the fæces, urine, bile and to a less extent in the milk, saliva and sweats.

Lead up to 0.02 and 0.18 mg. per thousand in urine and in fæces is normal (obtained from food). *Bagchi (1937)*.

SUMMARY.—Lead salts can precipitate protein and applied externally as hæmostatic and astringent on the bruised skin and the chronically inflamed mucous membranes. It is not used internally : toxic symptoms caused are due to powerful contractions of the unstriated muscles.

CHRONIC POISONING.—Very little of lead is absorbed from the usual therapeutic external administration to produce any systemic effect. But from prolonged contact with it or inhaling it for many weeks or months, as in different industrial workers, a sufficient amount may be absorbed and accumulated, to produce symptoms of *slow poisoning*. Women and children are more liable and a previous lead poisoning and alcoholism predispose. In such cases, the excretion of lead is slow and intermittent, traces appearing from time to time in the urine and fæces. The greater part of the retained lead is deposited in the bones, gums and to a less extent, in the liver and kidneys. The symptoms are, slowly progressing *anæmia* often aplastic, some of the red blood cells showing punctate basophilia : *blue line in the gums* from a deposit of lead sulphide and spasmodic contraction of *unstriated muscle-fibres* all throughout the body from direct action on these muscles. Thus on the alimentary canal, lead causes loss of appetite, metallic taste in the mouth followed by *colic* and obstinate *constipation* : on the uterus, *dysmenorrhœa*, *menorrhagia* and if pregnant, *abortion* ; on the cardiovascular system, vasoconstriction leading to arteriosclerosis and *high blood pressure*, increased cardiac tone with diminished relaxation leading finally to cardiac inefficiency. The *striated muscles* are also affected these being easily fatigued.

There may also be *paroxysmal pain* in the bones and joints (arthralgia) often worse at night.

In some cases the *nervous system* is more damaged. Most of the muscles supplied by the radial nerve beyond the triceps are paralysed leading to wrist drop. Less commonly, epileptiform convulsions (encephalopathy), loss of memory, disturbances of speech, muscular weakness, staggering gait are seen. There may be degenerative changes in the retina leading to blindness and also changes in the *kidneys*, ending finally in uræmia and death.

Treatment.—The source of intoxication is quickly removed. The bowels are opened with repeated doses of magnesium sulphate. Lead in circulation is made to collect in the bones by giving a plenty of calcium and phosphorus. This relieves the immediate symptoms and then the depot in the bones is depleted : see Calcium p. 273.

ARGENTUM, Silver, *Raupya*, *Tara*

1. ARGENTI NITRAS (*Argent. Nit.*), Silver Nitrate, Lunar caustic, AgNO_3 .

Silver Nitrate is prepared by the action of nitric acid on silver. Colourless, tabular crystals with no smell but bitter metallic taste. It is soluble at 15.5° in 0.5 of water, in 14 of alcohol (90%) and feebly in glycerin. It contains not less than 99.8% of AgNO_3 .

It must be kept in dark or wrapped with black paper as it is blackened on exposure to light.

ARGENTI NITRAS INDURATUS (*Argent. Nit. Indur.*), Toughened Caustic—Prepared by fusing together silver nitrate 19 and potassium nitrate 1 and moulded into cylindrical rods or cones. Contains between 94 to 96% of AgNO_3 .

INCOMPATIBLES.—Alkalies and their carbonates, chlorides, iodides, solution of arsenic, acids (except nitric and acetic) and tannic acid.

2. ARGENTOPROTEINUM, (*Argentoprot.*), Argentum-Proteinicum Forte, Strong Silver Protein.

Strong protein silver is prepared by the action of a silver compound on gelatin in the presence of an alkali. It contains between 7.5 to 8.5% of silver. Popular commercial preparation is *Protargol*.

A brownish, somewhat hygroscopic, inodorous powder, soluble at 15.5° in about 2 of water : insoluble in alcohol (95%), ether and in chloroform. Should be kept in a well-closed container protected from light.

The solution for use should be freshly prepared and dispensed in ambercoloured bottles.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, silver nitrate acts like a heavy metal but more powerfully than lead. Thus, it is **caustic**, **hæmostatic** and **astringent** by coagulating albumin. It is not only fixed up by protein but also by chlorides in the tissues and therefore gets inactivated in the superficial tissue and cannot penetrate deep enough. [Silver nitrate, popularly called lunar caustic, is locally applied as a "stick" for limited corrosive action. It at first forms a white coating of silver albuminate which on exposure to light, turns brown and finally black. It is used to cauterise bites of animals, a small septic wound or hypergranulation, to destroy warts and stop capillary bleeding as from a leech-bite].

In dilute solution, *Silver nitrate* is an **antiseptic** and **astringent** [and is therefore used in many kinds of subacute and chronic inflammation. In 1 in 400 to 1,000 solution, it was prescribed as wash for the urethra in chronic gonorrhœa and for the lower bowels in chronic bacillary dysentery but is not now so much used.

This in 1% solution is used for purulent ophthalmia²⁸⁴ also used as prophylactic to a newborn baby. In stronger solution,

(284) B

Argent. Nit. gr. 4

Aq. fl. oz. 1

A mild astringent for the eye,
also for bed-sores.

it is used as a throat paint in chronic pharyngitis²⁸⁵. A 5% solution in spirit of nitrous ether is used as paint in chronic eczema and as a **hardening agent** to prevent bed sores. As an antiseptic, it has about half the disinfectant efficiency of mercury salts, but the disadvantages are many more. It is irritant and its action is limited on account of its precipitation by chlorides and protein.

A silver nitrate solution becomes black or brown on exposure to light. [so a **hair dye**²⁸⁶ has been prepared with it]. A lotion should be kept in coloured bottles.

For **burns**, after applying 5% fresh tannic acid solution, 10% silver nitrate is applied: a dry eschar is formed immediately.

The *organic* (colloidal) *preparations* are less irritant and many are not inactivated by chloride or protein but are **slow** and **feeble antiseptics**.

These organic compounds are divided into four groups.—

(i) *The Proteinates*: the mild silver protein of argyrol type (20-25% of silver) are non-irritant and not precipitated by chlorides but are feebly ionized; used in 5 to 50% solution, often as argyrol or silvol. The protargol or strong silver protein type (nearly 10% silver) are more irritant, precipitated by chlorides and more ionizable. Protargol is prescribed in 1 to 10% solution. These are used mainly for the treatment of infections of the mucous membranes in the eyes, throat and in the nose. (ii) *The collargol preparations*: these contain over 70% of silver but not much free ion and are non-irritating. Collargol is an example. These are consequently suitable for administration on the mucous membranes and have slow but sustained bacteriostatic action. Applied in 0.1 to 2% solutions, further spread of the infection is stopped and this enables the body tissues to slowly destroy the infective organisms. (iii) *The electric type* as electrargol and (iv) *Silver halides* as neosilvol.

[These are frequently applied either as lotion, suppository, bougie, ointment into various mucous surfaces especially for gonorrhœa and ophthalmia]. Newer antiseptics, sulphonamides and antibiotics are throwing these into the back-ground.

SYSTEMIC ACTION of silver has been investigated by giving subcutaneous or intravenous injection of silver albuminate. The main action is on the medulla, which is at first stimulated shown by slowing of the pulse and the rise of blood pressure: afterwards paralysed: the blood pressure falls, the respiration becomes laboured and finally death takes place.

(285) R

Argent. Nit. gr. 15
Cocain. Nit. gr. 5
Aq. ad. fl. oz. 1

A throat paint.

(286) R

(Sol. 1): Argent. Nit. 1

Aq. 13

(Sol. 2): Potass. Sulphur. 1

Aq. 8 (Martindale)

Hairs washed and dried, first No. 1 and then No. 2 lotions applied. The hairs are washed again with soft water.

The mucous membranes of the bronchi and as with other heavy metals, of the stomach and intestine and also the kidneys are found congested.

INTERNALLY, silver nitrate is seldom used for any purpose. When taken orally, it acts as a **gastro-intestinal irritant** and coagulates albumin. [It was formerly used internally in gastric ulcer and obstinate diarrhœa for its local astringent action and also in nervous diseases as chorea, epilepsy and tabes but it is of no definite value and if continued long, causes symptoms of poisoning and it is not now used]. It is slowly absorbed and precipitated in the tissues as chloride or proteinate.

It is *slowly excreted* with fæces. A minute quantity may be retained and cause a fairly lasting slaty colouration of the mouth, gums and the skin, called **argyria**. This colouration is due to precipitated silver in the superficial tissue changed from exposure to light.

An *acute poisoning* is treated by a copious drink of saline solution : after vomiting, demulcent drinks are given and finally a dose of castor oil.

SUMMARY.—Silver salts are (i) *inorganic* (nitrate) or (ii) *organic* preparations used externally only as **astringent-antiseptic** and the nitrate, as **caustic** also but inactivated by protein and chloride. Organic preparations are less inactivated and non-irritant but slow in action : especially suitable for affection of the mucous membranes.

COMMERCIAL PREPARATIONS

ALBARGIN (Silver Gelatose), contains 15% of silver, soluble 1 in 2 of water : Lotion (1 in 500) is used in gonorrhœa and bacillary dysentery for irrigation²⁸⁷ : a stronger solution may be given as eye drop.

ARGYROL (called VITELLIN), a vegetable protein compound of silver, contains 20% of silver, freely soluble in water. For ophthalmia, 2 to 25% solution as eye drop and for colitis $\frac{1}{4}$ to 1% solution for irrigation.

CHOLEVAL, (Colloidal Silver with sodium cholate) is said to be unaffected by protein and is used in gonorrhœa as urethral or vaginal wash, 0.1 to 1% solution.

COLLARGOL (Colloidal Silver), freely soluble in water but does not make a clear solution : was sometimes given intravenously in $\frac{1}{4}$ to 1% solution for pyogenic infections but is of doubtful value. Lotions, suppositories and ointments²⁸⁸ of 1 to 10% strength are sometimes prescribed.

ELECTRARGOL, (Colloidal Silver), a reddish brown solution, containing 0.025% of silver, is used intramuscularly and also intravenously, in 1 to 10 c.c. doses in various infective conditions.

PROTARGOL²⁸⁹ (Silver Protein compound), contains 8 to 10% of silver : lotions and ointments from $\frac{1}{2}$ to 5% strength are used. It slightly stains the conjunctiva : further, it precipitates alkaloids as cocaine.

SILVOL and NEOSILVOL are milder preparations of silver and used in 5 to 10% solution on the mucous membranes.

- (287) R
Albargin gr. 16
Aq. one pint.
For bowel or urethral wash.
(288) R
Collargol 15
Adeps Benz. 75

- Cera Alb. 13
For gonorrhœa, prophylactic.
(289) R
Protargol gr. 10
Aq. Dest. fl. oz. 1
Lotio : Eye drop.

ZINCUM, Zinc, *Yasada, Dasta*1. ZINCI OXIDUM, (*Zinc. Oxid.*), Chinese white, ZnO .

White or faintly yellow, amorphous, inodorous and tasteless powder, insoluble in water prepared by the combustion of metallic zinc in air. It contains about 99% of ZnO .

Zinc oxide is used in the preparation of *Lot. Calamin.* and *Supp. Hamam. et Zinc. Oxid. Co.*

OFFICIAL PREPARATIONS.—(i) *Gelatinum Zinci* (*Gelat. Zinc.*), *Unna's paste*. : See p. 50. (15%). (ii) *Pasta Zinci Oxidi Composita* (*Past. Zinc. Oxid. Co.*), See p. 52. (25%). (iii) *Unguentum Zinci Oxidi* (*Ung. Zinc. Oxid.*), See p. 63. (15%). (iv) *Unguentum Zinci Oxidi Aquosum* (*Ung. Zinc. Oxid. Aquos.*), See p. 63. (15%).

2. ZINCI STEARAS (*Zinc. Stear.*), Zinc Stearate.

Prepared by the interaction of a soluble zinc salt and a solution of sodium salt of stearic acid. This has zinc stearate with zinc palmitate and has an equivalent of 13 to 15.5% of ZnO . A light white, fine, amorphous powder, having a faint fatty smell : insoluble in water, alcohol (90%) and in solvent ether.

3. ZINCI SULPHAS (*Zinc. Sulph.*), Zinc Sulphate, $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

Prepared by the interaction of zinc and sulphuric acid : it should contain 99.5 to 101% of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

Colourless transparent, inodorous crystals or crystalline powder with a metallic astringent taste. Soluble in less than 1 of water, making an acid solution.

DOSE, 10 to 30 grains or 0.5 to 2 grammes (as emetic).

INCOMPATIBLES.—Alkalies and their carbonates, lead acetate, silver nitrate and tannic acid.

OFFICIAL PREPARATIONS.—*Unguentum Zinci Oleatis* (*Ung. Zinc. Oleat.*), See p. 63. (5.2%).

4. CALAMINA (*Calamin.*), Calamina Præparata.

Calamine is basic zinc carbonate, suitably coloured with ferric oxide which gives reddish brown or pink colour to this amorphous powder, insoluble in water. Soluble in hydrochloric acid causing effervescence.

Lotio Calaminæ (*Lot. Calamin.*), See p. 50. (15%).

Pharmacology [and Therapeutics]

Zinc-ion has the usual general properties of heavy metals but it is less powerful than either lead or silver-ion. Of the salts, the *chloride* is much more powerful and is a strong caustic but the *sulphate* and the *acetate* are weaker and are only astringent and hæmostatic. The *oxide* is weaker still. The chloride is sometimes used as a paste or made into pencil for destroying localised growths. The sulphate is frequently made into $\frac{1}{2}\%$ lotion, *Lotio Rubra*²⁹⁰ and used for its

(290) B

Red Lotion.

Zinc. Sulph. gr. 2

Tinct. Lavand. Co. min. 10

Aq. ad. fl. oz. 1

astringent effect on various mucous surfaces as in conjunctivitis²⁹¹, otorrhœa, chronic gonorrhœa²⁹² and in leucorrhœa. Less commonly, this with sulphurated potash, each 90 grains, in 4 oz of water, called *Lotio Alba*, is used for acne vulgaris.

The oxide is made into dusting powder²⁹³ with equal parts of boric acid and starch or talc (magnesium silicate) and this and also the stearate are made into ointment for various chronic skin affections^{294, 295}. This and calamine (a mixture of zinc carbonate and oxide) are made into lotions for an irritable condition of the skin as in the acute stage of eczema or of an eruptive fever^{296, 298}.

INTERNALLY, none of these is used. The sulphate is a mild irritant: this causes immediate vomiting by irritating the mucous membrane of the stomach and 20 to 30 grains in 6 to 8 fluid oz. of water, are sometimes given to cause prompt vomiting in a case of poisoning. It was formerly used as a nerve sedative in various affections as in *hysteria* especially zinc valerianate²⁹⁹, but it is not of any substantial value.

Symptoms of *chronic poisoning* are sometimes seen in workers of brass foundry. These are, progressive weakness, metallic taste in the mouth, nausea and vomiting: sore throat, cough and pain in the chest: muscular cramps, headache, somnolence and quick feeble pulse.

SYSTEMIC ACTIONS of the zinc-ion are produced when a double salt is given hypodermically or intravenously to an animal; vomiting, diarrhœa, tremors and finally paralysis of the central nervous system follow.

- (291) R
Zinc. Sulph. gr. 1
Liq. Plumb. Subacet.
Dil. fl. oz. 4

For urethral injection.

- (292) R
Zinc. Sulph. gr. 2
Acid. Boric. gr. 10
Aq. ad. fl. oz. 1
Lotion. For chronic conjunctivitis.

- (293) R
Zinc. Oxid.
Acid. Boric aa. gr. 60
Talc. gr. 320

A good dusting powder.

- (294) R
Zipp.
Zinc. Oxid. 2
Iodof. 2
Paraff. Liq. 2 to 3
Pasta for a septic wound.

- (295) R
Zinc. Stear.
Plumb. Oleat. aa. gr. 20
Hydrarg. Oleat. min. 20
Paraff. Moll. Alb. ad. oz. 1
Ung. For chronic eczema and psoriasis.

- (296) R
Zinc. Oxid. gr. 180
Ichtham. min. 10
Adeps Lan. gr. 240
Liq. Calc. Hydrox.
Ol. Oliv. aa. fl. oz. 1
For eruptive fevers.

- (297) R
Calamin. gr. 40
Zinc. Oxid. gr. 20
Glycer. min. 15
Liq. Calc. Hydrox. min. 180
Aq. Rosæ ad. fl. oz. 1 or 2
For acute stage of eczema or seborrhœa.

- (298) R
Calamin. 10
Zinc. Oxid. 5
Zinc. Stear. 2.5
Adeps. Lan. 2.5
Paraff. Moll. Alb. 20
Paraffin. Liq. to 100
Emollient astringent cream.

- (299) R
Pil. Aloes et Asafoet.
Zinc. Valerian aa. gr. 2
Ext. Gent. q.s.
Pil. For hysteria.

SUMMARY.—*Zinc chloride* is **caustic** : *sulphate* is astringent-antiseptic and is frequently applied for inflammatory affections of the **mucous membranes** also occasionally as an emetic. Insoluble preparations as *carbonate* (as calamine), *oxide*, *stearate* and *oleate* are used externally only as lotion, dusting powder, cream or ointment for irritating condition in the skin.

Non-official Preparations

ZINC CHLORIDE.—Colourless rods or crystals used as caustic : in $\frac{1}{2}$ to 1% lotion, it is astringent.

ZINC TANNATE.—A non-irritating, mildly astringent dusting powder,

ZINC CARBONATE is also similarly used.

ZINC VALERIANATE.—In 1 to 3 grs. doses is sometimes given in hysteria.

LASSAR'S PASTE.—Zinc oxide 24, starch 34, salicylic acid 2, vaseline 50 : mix. For chronic eczema.

CALIGESIC.—Calamine 8 g., benzocaine 3 g., hexalated metacresol 0.05 g. and a non-fatty base to 100 g. An ointment for painful irritating surface.

CUPRUM, Copper, *Tamra*

CUPRI SULPHAS, (Cupr. Sulph.), Copper Sulphate, Blue vitriol : *Tutia*, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$.

Prepared by the action of sulphuric acid on copper in the presence of water, containing between 98.5 to 101% of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. Blue, triclinic prisms or a blue crystalline powder. Soluble in 3 of water and in 3 of glycerin. Solution is neutral in reaction.

DOSE, as an *astringent*. $\frac{1}{4}$ to 2 grains or 16 to 120 mg. As an *emetic*, 5 to 10 grains or 0.3 to 0.6 gramme.

INCOMPATIBLES.—Alkalies and their carbonates and oxides, mineral salts (except sulphates), iodides and tannic acid.

Pharmacology [and Therapeutics]

SYSTEMIC ACTION is shown when a double salt is given hypodermically or intravenously. It depresses the central nervous system and to a less extent the heart and voluntary muscles (causing paralysis) and like other heavy metals, causes irritation of the stomach, intestine and the kidneys. Death follows from respiratory paralysis.

APPLIED LOCALLY, like other heavy metals, copper salts have the power of precipitating protein and therefore the sulphate has the usual **caustic**, **astringent** and **hæmostatic properties**³⁰⁰. [It is frequently applied to destroy the exuberant granulation tissue of a healing wound and less commonly, like zinc sulphate, it is used as a lotion³⁰¹ for various inflammatory conditions of the mucous membrane].

It is an **antiseptic** also especially to certain lower forms of life such algæ even in 1 in 50,000,000 solution and is sometimes

(300) B

Lapis Divinus.

Cupr. Sulph.

Alum.

Pot. Nit. aa gr 60

Fuse together and add Camphor

1 or less. Astringent, caustic and hæmostatic.

(301) B

Cupr. Sulph. gr. 2

Aq fl. oz. 1

Astringent lotion.

used in water reservoirs. Cupric citrate is sparingly soluble and 5 to 10% of it is made into eye ointment for trachoma.

TAKEN INTERNALLY, copper sulphate is a **prompt emetic** for its direct irritant action on the stomach. As the salt is quickly removed, it causes no damage to the mucous membrane. [5 to 10 grains in 2 to 4 fluid oz. of water it is occasionally used as emetic in cases of poisoning. It is especially useful in phosphorus poisoning as the sulphate radicle oxidises phosphorus to phosphate and free copper is deposited on phosphorus which prevents absorption. But if it fails to act, it may cause severe inflammation of the stomach]. In smaller doses it is an **astringent** : [it was formerly given in $\frac{1}{4}$ grain doses in obstinate diarrhoea but is not used now].

Taken in bigger doses accidentally or for suicide, it may cause severe gastro-intestinal irritation with abdominal pain, vomiting and diarrhoea, vomit and stools being of bluish or greenish colour and finally collapse sets in ending fatally : the mucous membrane of the stomach and intestine may be corroded.

Treatment.—Stomach washing or emetic is not usually necessary : warm water may be given in plenty. Solution of egg albumin, milk, tannic acid, magnesia and potassium ferrocyanide are antidotes.

It has been claimed that a minute quantity of copper is required with iron to form hæmoglobin and the two together are better hæmatinic than iron alone. (Hart and Steenbock, 1928). It has also been found that in rat experiments, iron taken is stored in the liver but is not made to hæmoglobin without copper (Cunningham, 1931). It is not yet definitely known how copper acts : it takes no part in the absorption or storage of iron : may have a catalytic action. It is thought that to maintain the normal hæmoglobin level, the food must contain at least 3 mg. of copper daily.

Green vegetables and liver have some copper and these are the usual source : cow's milk is especially deficient.

In adult anæmia, copper deficiency is not usually a factor but in infants³⁰² on milk feeds copper should be given along with iron. Three mg. of copper sulphate daily for an infant is the usual dose.

The absorbed copper is partly stored in the liver, spleen, kidneys and the thyroid : the balance is excreted by the intestine and the kidneys. It passes from the mother to the foetus.

(302) B

Ferr. et Ammon. Cit. gr. 20

Cupr. Cit. gr. $\frac{1}{4}$

Sp. Chlorof. min. 15

Aq. Anis. ad. fl. oz. 1

One tea-spoonful with milk.

SUMMARY.—Copper sulphate is used as a **caustic** and in a dilute solution, as **antiseptic-astringent** : in minute doses *orally*, may be **hæmætic** : it is not a safe emetic.

Non-official Preparations

COLLOIDAL COPPER, in 1 to 5 c.c. dose has been given intramuscularly twice a week in Hodgkin's disease.

CUPRI OLEAS is made into ointment³⁰³ for mild antiseptic and astringent action.

CUPRI CITRAS, in 1/20 to 1/10 gr. doses is given with an iron preparation for hypochromic anæmia.

CUPRELONE, cuproallyl thiourea-meta sodium benzoate (has 19% of copper) is given intravenously in increasing doses of 10 to 100 mg. twice a week (total dose is 2.5 to 5 g.) : interval of a month is given between the first two courses and then 2 to 3 months : useful in rheumatoid arthritis and lupus erythematosus.

CUPRO-OXYQUINOLINE-SULPHON METHYLAMINE in aqueous solution, 0.5 g. 2 or 3 times weekly, till 6 to 9 g. in 12 to 18 injections, makes a course : repeated after one month : useful in rheumatoid arthritis.

ALUMINIUM

ALUMEN (*Alum.*), Purified Alum, Potassium Aluminium Sulphate or Potash Alum, $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ and Ammonium Aluminium Sulphate or Ammonium Alum, $\text{NH}_4\text{Al}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ *Sphatikari*.

Prepared by combining aluminium sulphate with potassium or ammonium sulphate : strength is 99.5%. Colourless, transparent octahedral crystals or powder with a sweetish astringent taste. Very soluble in water and freely in glycerin but insoluble in alcohol.

INCOMPATIBLES.—Alkalies, salts of lead, mercury and iron, tartrates and tannic acid.

KAOLINUM and its preparation, **CATAPLASMA KAOLINI**, have already been described. (See p. 140).

Pharmacology [and Therapeutics]

Alum (Potassium aluminium sulphate) is **not caustic** on the unbroken skin except moderately, in desiccated form but on an abraded area and also on various mucous surfaces it acts as a local **astringent** and **hæmostatic**. The sulphate, acetate and the chloride are fairly powerful **antiseptics** also. [These are therefore frequently used as gargle for various chronic inflammatory conditions in the mouth, throat and tonsils³⁰⁴. A $\frac{1}{2}$ per cent solution is sometimes used as eye lotion³⁰⁵ alone or with zinc sulphate. The same may also be used as an urethral and vaginal wash. In a concentrated solution

(303) B

Cupr. Oleat. 12

Paraff. Moll. Alb. 88

Ung. For ringworm.

(304) B

Glycer. Alum. min. 240

Aq. Rosæ fl. oz. 8

A gargle for chronic pharyngitis.

(305) B

Alumen gr. 2

Aq. Rosæ fl. oz. 1

Eye lotion.

or in powder form, it is applied on superficial bleeding spots and on piles].

INTERNALLY, Alum has a sweet **astringent** taste and in large doses **emetic** but is not used for any such purpose.

In 30 grains doses, it is of some value in acute lead poisoning, lead is precipitated as insoluble sulphate but magnesium sulphate is more preferable.

Aluminium hydroxide is an **antacid** without causing systemic alkalisation (See p. 141). Aluminium phosphate may also be used in the same way as tablets, powder or gel.

Aluminium salts taken orally for some time are absorbed and cause toxic symptoms. The use of aluminium cooking vessels is however free from danger (Burn). Alum is used in baking powder and sometimes in the preparation of whey but no systemic poisoning follows therefrom.

SUMMARY.—Aluminium sulphate is an **astringent-antiseptic** and **hæmostatic** of moderate intensity and is used on the mucous membranes.

Non-official Preparations

ALUMNOLE (aluminium naphthol sulphonate), ALSOL (aluminium acetate), BORAL (aluminium borotartrate), CUTOL (aluminium borotannate), GALLOL (aluminium gallate) and SALUMEN (aluminium salicylate) are sometimes used as astringent dusting powder and sometimes as lotion.

GLYCERINUM ALUMINIS.—Potash alum 130, distilled water 60 and glycerin to 1000.

BENTONITE, native colloidal hydrated aluminium silicate is used as *sols* for suspending insoluble powders (2% for light and 5% for heavy powders) and as *gels*, 2% of bentonite makes oil-in-water emulsion and a 5% of it with 10% glycerin makes water soluble ointment base.

GOLD

SODII AUROTHIOMALAS, (*Sod. Aurothiomal.*).

Sodium Aurothiomalate is mainly the sodium salt of aurothiomalic acid, prepared by the interaction of gold iodide and sodium thiomalate, precipitation of sodium aurothiomalate by adding sodium chloride and subsequent purification. Contains 44.5 to 46% of Au and between 10.8 11.3% Na of the substance dried in vacuo over sulphuric acid.

A fine pale yellow nearly inodorous, hygroscopic powder, very soluble in water.

Dose by intramuscular injection, $\frac{1}{2}$ grain increasing gradually to $1\frac{1}{2}$ grains or 10 mg., increasing to 100 mg. weekly.

Injectio Sodii Aurothiomalatis (*Inf. Sod. Aurothiomal.*), See p. 46. Strength is 10 mg. per ml. or $\frac{1}{6}$ gr. in 15 min.

Dose as of sodium aurothiomalate.

Pharmacology [and Therapeutics]

Gold preparations have a limited therapeutic use.

Gold salts are **local irritants**. Taken orally, a soluble salt is a gastro-intestinal irritant. Given *intravenously*, it dilates the mesenteric blood vessels and causes a fall in blood pressure.

Sodium aurothiomalate (*Myocrisin*) was used for the treatment of **pulmonary tuberculosis** but being of not much value is no longer used.

It is of some value in **rheumatoid arthritis** and **fibrositis** given intramuscularly in watery solution (occasionally in suspension in oil) in increasing doses commencing from 0.01 g. weekly, to 0.05 g. total about 0.5 g. in 10 to 12 weeks. There may be temporary fever with focal reaction. Blood sedimentation rate (which is increased in arthritis) should be periodically estimated.

It is also used in **lupus erythematosus** and other dermatoses in the same dose. Localised afebrile conditions are suitable for treatment.

TOXIC SIGNS.—The drug is toxic to *skin, mucous membranes, kidneys, hæmopoietic and nervous systems*. These are pruritis, skin rashes, stomatitis, albuminuria and hæmorrhagic state : rarely toxic hepatitis, aplastic anæmia and agranulocytosis.

COMMERCIAL PREPARATIONS.—In addition to myocrisin, **SANOCRYLIN** (thiosulphate of sodium and gold) : *Dose*, 0.05 to 1.5 g. **SOLGANOL B OLEOSUM**, *Dose*, 0.01 g. or less, slowly increased to 0.1 g.

OTHER METALS

(i) **TIN.**—Chloride is sometimes given as antispasmodic (*Dose*, $\frac{1}{6}$ to $\frac{1}{2}$ gr.). **STANNOXYL** tablets (metallic tin and tin oxide), 4 to 6 were given daily for superficial boils, now replaced by sulphonamides.

(ii) **CERIUM.**—Oxalate (*Dose*, 3 grs.) and Nitrate are given for vomiting^{306, 307} especially of pregnancy but of doubtful value.

(iii) **THALLIUM.**—Thallium acetate is used as *depilatory* (p. 185) in ringworm infection.

COLLOIDAL METALS

In 1861, Graham divided soluble substances into crystalloids and colloids according to whether they do or do not pass through a piece of parchment. The term 'colloid' therefore means a physical state.

A substance in suspension or emulsion tends to sediment if the size of its individual particles is 0.1μ (1/10 micron) or bigger. But if smaller and up to 0.001 micron or one $\mu\mu$, they remain in suspension or in colloidal state and do not sediment. In still smaller division, however, they pass into solution.

Some colloids, as gelatin or albumin, attract the solvent as water and get more or less liquefied. But others, as the colloidal metals, have no such affinity and remain solid. The latter are kept apart in suspension by the molecular movements of the particles (Brownian movements). These are charged with electricity, positive or negative and as all the particles have the same kind of electrical charge, they repel one another which prevent clumping.

PROTECTION.—All metallic colloidal suspensions require protection by some organic colloids as gelatin, albumin, glucose, etc., otherwise they

(306) B

Cer. Oxal. gr. 3

Chlorbut. gr. $2\frac{1}{2}$

Menthol gr. $\frac{1}{2}$

Lactos. gr. 5

Pulv. For vomiting of pregnancy

(307) B

Hydrarg. Subchlor. gr. $\frac{1}{2}$

Cer. Oxal. gr. 2

Benzocain. gr. 1

Glyc. Trag. q.s.

Pil. For bilious vomiting.

soon lose their colloidal character. Therefore the former are prepared in combination with the latter.

A colloidal solution is prepared chemically as by fractional sedimentation or electrically, by passing an electric current through two metallic wires under water or by using high frequency alternating current.

Applied locally, colloids are non-irritant and antiseptic only on prolonged contact. *Given by subcutaneous or intravenous injection*, these are gradually transformed into ionic condition in the system and are therefore capable of producing slow and sustained metallic action. These are also believed to be catalytic agents capable of inducing chemical changes in other substances, they themselves not undergoing any transformation.

Antimony, arsenic, calcium, copper, gold, iron, lead, manganese, mercury, platinum, silver and also sulphur have been made into colloids and used both orally and by intramuscular injection.

METALLIC PREPARATIONS IN AYURVEDA

Hindu Physicians introduced mineral preparations in practice long before their colleagues in other countries. They did not know the preparation of mineral acids and so had to depend on natural metallic products. They, however, prepared oxides and sulphides by calcination and sublimation and also organic salts by soaking metals in vegetable and other natural acids.

A large number of metals were used. Preparations of sodium, potassium and calcium were used externally as caustic and internally in various gastro-intestinal disorders and as diuretic (also for stone in the kidneys). Heavy metals were used externally as caustic, depilatory, astringent and hæmostatic. Internally, various combinations of arsenic, mercury, gold, iron, silver, copper, tin, zinc, lead and aluminium were used. In such ancient records as of about 1066 A.D. they were found to handle highly toxic drugs like mercury and arsenic with remarkable therapeutic skill.

Mercury, arsenic, gold, iron and other metals were believed to be tonic and alterative in many cachectic conditions including tuberculosis. Arsenic was also used for intermittent fevers coming with rigor. Tin was found useful in cystitis. Aluminium silicate was used for hyperacidity. Their various combinations were prescribed practically in all kinds of diseases.

X. DRUGS ACTING ON THE NERVOUS SYSTEM

1. Drugs acting on the Central Nervous System

The central nervous system includes the *cerebrum*, *midbrain*, *medulla* and the *spinal cord*. The drugs acting therein may either be *excitatory* or *inhibitory* and the inhibitory action is more often of practical therapeutic value.

(i) THE CEREBRAL DEPRESSANTS include a large group which is arbitrarily subdivided into *exhilarant intoxicants*, *general anæsthetics*, *hypnotics*, *narcotics*, and *analgesics*; the actions of many in different items often overlap.

(a) *Exhilarant Intoxicants*.—The alcohol group is more important.

(b) *General Anæsthetics*.—If *volatile*, are administered by inhalation as chloroform, ether, divinyl ether, cyclopropane nitrous oxide, ethylene, ethyl chloride and trichloroethylene. These cause *surgical* or *complete anæsthesia*. If *nonvolatile*, are

given per rectum or by injection as paraldehyde, bromethol, hexobarbitone, phenobarbitone, pentobarbitone and thiopentone also scopolamine-morphine. These cause partial anæsthesia (*basal anæsthetics*).

(c) *Hypnotics* (*G. hypnos*, sleep) are drugs that cause sleep. These cause primary depression of the upper cerebral centres without a stage of excitement and the effect lasts for a few hours. *Sedation* is a milder degree of hypnosis: the patient is awake but quiet. These include a large group: bromides, chloral group, sulphonal, barbiturates, urethane and paraldehyde.

(d) *Anticonvulsants* are muscle-relaxants administered during active convulsions. These are phenytoin sodium, mesantoin, tridione, barbiturates, bromides and basal anæsthetics.

(e) *Narcotics* (*G. narke*, numbness) are drugs that lessen perception causing a feeling of lethargy (sometimes of a pleasing nature, *euphoria*, of some duration) which with a bigger dose, causes analgesia, may pass on to hypnosis and unconsciousness. Opium group, cannabis indica and alcohol may be included here.

(f) *Analgesics* (*G. an*, without and *algos*, pain) are drugs that relieve pain without causing stupor or unconsciousness. These are morphine group acting centrally: pethidine and other synthetic analgesics and coal tar analgesics (phenazone, phenacetin, amidopyrine and acetylsalicylic acid: these are somewhat antipyretic also). These act on the **subthalamie region**.

(ii) THE CEREBRAL STIMULANTS increase the *mental activities*: sometimes causes *wakefulness* or *delirium*. Caffeine, amphetamine, leptazol, nikethamide, camphor, picrotoxin, cocaine, strychnine and belladonna may be in this group.

CONVULSANTS.—Several others given in big doses, increase the *motor activities* without volitional control.

(a) *Cerebral convulsants*: a limited group of muscles are involved in irregular movements: the drugs are atropine, essential oils, cocaine and santalin.

(b) *Brain-stem convulsants*: clonic, irregular movements are caused: the drugs are strychnine, camphor, picrotoxin, ether (occasionally), ammonium salts and asphyxia, also insulin, leptazol and nikethamide in big doses intravenously.

(c) *Spinal convulsants* cause symmetrical tetanic convulsion: these are strychnine, thebaine, morphine (occasionally in children), caffeine, calabarine and filicic acid in toxic doses.

(iii) MEDULLARY STIMULANTS increase the cardio-respiratory centre activities: leptazol, nikethamide, picrotoxin, caffeine, strychnine, ammonia and CO₂ are in this group. The *Inhibitors* are cyanides and over dose of hypnotics and general anæsthetics: opium is markedly depressant to the respiratory centre.

Apomorphine stimulates the vomiting centre causing emesis.

(iv) SPINAL CORD STIMULANTS or DEPRESSANTS act mainly on the motor functions causing either convulsion (p. 443) or muscular paralysis.

2. Drugs acting on the Peripheral Nerve Endings

(i) Drugs paralysing the *sensory nerve endings* are cocaine, procaine, amethocaine, amylocaine, butacaine, cinchocaine, benzocaine, butylaminobenzoate and orthocaine : also benzyl alcohol and magnesium sulphate.

(ii) Drugs paralysing the *motor nerve endings* are curare group also coniine, gelseminine and sparteine.

3. Drugs acting on the Autonomic Nervous System

(i) Drugs acting on the *autonomic ganglia* are of the nicotine group.

(ii) Drugs *stimulating the parasympathetic nerve endings* are muscarine group, choline group, physostigmine, neostigmine and pilocarpine.

(iii) Drugs *depressing the parasympathetic nerve endings* are atropine group and synthetic belladonna alkaloid substitutes.

(iv) Drugs *stimulating the sympathetic nerve endings* are adrenaline, ephedrine, amphetamine and synthetic products.

(v) Drugs *depressing the sympathetic nerve endings* are ergotoxine and ergotamine.

I. ALCOHOL ETHYLICUM

Ethyl Hydroxide (Ethyl Alcohol, C_2H_5OH)

ALCOHOL (95%), *Alcoh.*, Alcohol.

Alcohol (95%) is a mixture of ethyl alcohol and distilled water, obtained by distillation of fermented saccharine liquids. Contains not more than 95.2% by volume and 92.7% by weight or less than 24.7% by volume and 22% by weight of C_2H_5OH .

It is a colourless, transparent, mobile liquid with a faint characteristic smell. It evaporates rapidly and is highly inflammable, burns with a blue smokeless flame and on evaporation, leaves no mark or residue. It mixes well with water, chloroform and solvent ether. It should have no fusel oil, methyl alcohol, aldehyde, ammonia or other organic impurities.

DILUTE ALCOHOLS

1. ALCOHOL 90%, Spiritus Rectificatus or Rectified Spirit.

Contains 90% by volume of ethyl hydroxide and 10% of water. Alcohol (95%) 947 ml. and distilled water to make 1000 ml. or one litre (1 l.).

2. ALCOHOL (80%).

Alcohol (95%) 842 ml. and distilled water to make 1000 ml.

3. ALCOHOL (70%).

Alcohol (95%) 737 ml. and distilled water to make 1000 ml.

4. ALCOHOL (60%).

Alcohol (95%) 632 ml. and distilled water to make 1000 ml.

5. ALCOHOL (50%).

Alcohol (95%) 526 ml. and distilled water to make 1000 ml.

6. ALCOHOL (45%).

Alcohol (95%) 474 ml. and distilled water to make 1000 ml.

7. ALCOHOL (25%).

Alcohol (95%) 263 ml. and distilled water to make 1000 ml.

8. ALCOHOL (20%).

Alcohol (95%) 210 ml. and distilled water to make 1000 ml.

Non-official Preparations

PROOF SPIRIT is one which "at a temperature of 51°F. weighs exactly 12/13th part of an equal measure of distilled water". Weaker spirits are called *under-proof* and stronger ones, *over-proof*.

Various commercial types of alcohol are available, usually used as beverage ; these are prepared as follows—

(i) **MALT LIQUORS**.—Prepared by fermenting with yeast, various starchy substances to which a bitter principle is often added for flavour. These contain 2 to 7% of alcohol. The well known preparation of this type is *Beer*.

(ii) **WINES**.—These are prepared by fermenting with yeast various sugar-containing fruit juices. The amount of alcohol is 5 to 15%. This group contains *Claret* and *Champagne*.

(iii) **FORTIFIED WINES**.—The wines are fortified or made stronger by addition of a distilled liquor. In ordinary fermentation, the yeast activity ceases at about the concentration of 15 to 17% of alcohol by volume and so an alcohol of higher strength can only be obtained by concentrating it by distillation.

Sherry, Port and *Madeira** are varieties of this group.

(iv) **DISTILLED LIQUORS** or spirits are prepared by distilling the fermented liquor. In the process of distillation of alcohols, ether and any volatile acid, if present, are also distilled over.

Stored for a long time, alcohol and acid react upon each other and develop esters which give flavour to the liquor. This is the reason why for medicinal purposes, old and mature wines are preferred. These may be divided into two groups :—

(a) Of those obtained by distilling malted liquors may be mentioned *Whisky* and *Gin*.† The latter contains extracts of juniper and cardamom and is a diuretic and carminative also.

(b) Of those obtained from sugared fruits, like grapes, the most important is *Brandy*. *Rum* is obtained by distilling molasses left in sugar-cane juice after sugar has been crystallised out.

LIQUEURS are spirits to which volatile oil flavourings have been added. *Absinthe* and *Vermouth* contain oil of Thujon and *Cocktails* are mixtures of various liqueurs, usually with gin.

FUSEL OIL.—The fermented sugar contains 95% of ethyl alcohol and 5% of various other substances as propyl, butyl and amyl alcohols : organic acids, aldehydes and esters. These collectively are called Fusel oil.

During distillation, these are also distilled over along with ethyl alcohol : so a freshly distilled alcohol should not be taken internally. When stored for some years, fusel oil is oxidised and esters are formed which improve the flavour and efficiency.

* *Madeira* and *Sherry* 16 to 22%.
Port 20 to 30%.

† *Whisky* and *Gin* 51 to 59%.
Brandy (*Spiritus Vini Gallici*) 43 to 57%.
Rum 51 to 59%.

Pharmacology [and Therapeutics]

The various preparations of dilute alcohol are *used internally* either as *beverage* or *stimulant* for causing euphoria and are always the mixtures of several substances, some of which are intentionally added as flavourings. But the preparations of stronger alcohols are not used internally as such. DEHYDRATED ALCOHOL (containing 99% by weight and 99.4% by volume of ethyl hydroxide), ALCOHOL 95% and RECTIFIED SPIRIT (alcohol 90%) are mostly *used externally* as *antiseptic* and *preservative* and also as *solvents* for various chemicals and pharmaceutical preparations.

The actions of ALCOHOL may be divided into two parts.

(i) **Local**, on the tissues it immediately comes in contact with.

(ii) **Systemic**, action after absorption, on the general metabolism and on the central nervous system.

1. THE LOCAL ACTION OF ALCOHOL.

(i) *On the Skin*.—A concentrated alcohol acts as an **irritant** by partial precipitation of albumin and absorbing water; the more the concentration is, the greater is the action but if the strength is below 40%, no obvious irritation is caused. A *raw surface* is more powerfully acted on than the intact skin: a 10 to 20% solution is astringent but a strong solution may cause tissue necrosis.

If allowed to evaporate, it so quickly disappears that no obvious irritation is caused: it **cools the part** causing constriction of the cutaneous blood vessels and slight **anæsthesia**. [Therefore it is used for reducing a local inflammation either from injuries^{308, 309} or disease and it not only lessens the inflammation but also the pain. With the same object it is often applied on the forehead for headache in the form of Eu-de-Cologne]. It is also a **refrigerant** lowering the temperature [and so it is occasionally used mixed with water for sponging a patient with high fever].

It **hardens the skin** by absorbing water [Alcohol (90%) is often applied daily to the pressure points of bed-ridden patients to prevent bed-sores³¹⁰ and also to the nipples of nursing mothers to harden these to prevent cracking].

If the evaporation is prevented by covering up immediately, or by quickly rubbing it in, it acts as **irritant** and **rubefacient**

(308) R *Lotio Evaporans*.
Liq. Ammon. Acet. min. 60
Ammon. Chlor. gr. 10
Alcohol (90%) min. 120
Aq. ad. fl. oz. 1

(309) R
Tinct. Arnica. Flor. min. 60
Sp. Methyl. Indus. min. 120
Aq. ad. fl. oz. 2

To apply on a sprain.

(310) R
Alum.
Sod. Chlor. aa. gr. 60
Alcohol (90%)
Aq. aa. fl. oz. 5 (Loomis).
To apply over a threatened bed-sore.
(Also useful for sore nipples and sweating of hands and feet).

by dilating the cutaneous blood vessels and if this is persisted longer, it causes inflammation and vesication. [It is therefore one of the constituents of many liniments used for local rubefacient effect].

It is an **antiseptic** also. But alcohol cannot penetrate into bacteria except in the presence of water. It has been estimated that alcohol 70% is the best disinfectant. If weaker, its activity is markedly lessened: if stronger the bacteria are desiccated but not killed. It dissolves fat and penetrates into sweat and sebaceous glands of the skin and disinfects its deeper layers also. [A moderately concentrated alcohol is therefore often used for sterilising the surgical instruments which would not be boiled and also applied on the skin, prior to minor surgical operations and injections. Various antiseptics, especially mercuric chloride dissolved in weaker alcohol (p. 305) is used for sterilising surgeon's hands. Alcohol penetrates into the skin and carries the antiseptic inside: with 2% of iodine, it forms a solution for sterilization of the skin in surgical operation]. But it lowers the efficiency of phenol which loses its local action on the skin. [Therefore, if applied immediately, it is an antidote to carbolic acid burn].

Injected subcutaneously, in concentration over 50%, it causes pain and injected into a nerve, causes its degeneration. [Alcohol 80% is sometimes injected into the nerve sheath in trigeminal neuralgia and in sciatica. The pain is relieved for several months till the nerve regenerates and sometimes the relief is more lasting].

(ii) *On the Mucous Membranes.*—

The local effects on the mucous membranes are obviously more powerful than those on the skin.

(a) **MOUTH.**—A more powerful **irritant** action than that on the skin takes place. Alcohol gives a feeling of warmth and if concentrated, burning sensation and also pallor with whiteness of the mucous membrane from coagulation of albumin. But as this coagulum is redissolved in the body fluid, it quickly disappears. [For this reason, it is sometimes added to different astringent mouth washes³¹¹ in stomatitis]. A 10% alcohol increases the flow of saliva by causing mild local irritation.

It stimulates the secretion of saliva and reflexly of the gastric juice and improves **appetite**. Almost simultaneously, the **pulse-rate** is also quickened and more quickened when alcohol reaches the stomach, by irritating the sensory nerve-endings there (*Cardio-acceleratory reflex*).

(311) B

Tinct. Myrrh.

Alcohol (90%) aa. min. 150

Aq. ad. fl. oz. 3

A gargle for stomatitis, pharyngitis and tonsillitis.

But if taken in concentrated form or in large amount, it diminishes the secretions by its local astringent action.

(b) **STOMACH.**—With a small dose and in diluted form (5 to 10%), the **gastric secretion** and **peristalsis** are increased which improve the appetite. This is further favoured by various flavouring agents of the liqueur as bitters in beer and ethereal esters in the wines. In addition to the reflex effect, this increase of secretion is partly direct after absorption of alcohol into the circulation and rectal administration also causes similar increase of secretion. The activities of the digestive ferment are somewhat interfered with but this is temporary as alcohol is readily absorbed. The increased gastric secretion caused by it favours digestion and also **promotes absorption** from the stomach and the intestine. [It is therefore useful as a **digestive** and is especially indicated during convalescence from prolonged illness and may be usefully combined with other digestives as bitters and pepsin^{2 13}. The acid portion of gastric secretion is more definitely increased but not pepsin. [Alcohol 5 to 7%. 50 c.c. has been used as a *test meal* for estimating the gastric acidity].

Taken in large doses or in concentration of 20% and over, especially if frequently repeated, it is harmful. It acts as an **irritant**: the gastric ferments are diminished and pepsin is precipitated; movement of gastric musculature is lessened. The mucous membrane is covered up with a protective mucous coating. This results in gastritis of the drunkards, finally leading to atrophy of the glands of the stomach.

(c) **INTESTINE.**—The local action of alcohol on the intestine is feeble as alcohol is considerably diluted by the time it reaches there, but brandy is believed to be slightly **astringent** [and may be of some use in diarrhœa^{3 13}].

II. SYSTEMIC ACTION AFTER ABSORPTION

(a) **STOMACH AND INTESTINE.**—A quarter of the alcohol taken, is quickly absorbed from the stomach and the rest from the upper part of the small intestine into the blood, reaching the maximum concentration in about 2 hours. It attains higher concentration in the plasma than in the corpuscles. But it disappears from the blood more slowly. A quantity equivalent to about 10 c.c. of dehydrated alcohol may be **oxidised** per hour in the body and in that process of combustion, it spares carbohydrate and fat and consequently also protein. The protein breakdown temporarily increases, being the immediate

(312) R
Glycer. Pepsin. min. 60
Tinct. Nuc. Vom. min. 10
Spiritus Vini Gallici min. 30
Inf. Gent. Co. ad. fl. oz. 1
For general debility, with poor
appetite.

(313) R
Sp. Camph. min. 10
Sp. Vin. Galic. min. 30
Mix: Given with a lump of
sugar, every 2 hours for summer
diarrhœa.

toxic action of alcohol. But tolerance is soon established, and alcohol takes the place of carbohydrate and fat for the supply of bodily energy : so the tissue waste is lessened and nitrogenous output in the urine falls. The fatness of the alcoholics is well known.

Alcohol is therefore an **easily oxidisable** food requiring no previous digestion and oxidation starts in 5 to 10 minutes after ingestion, supplying about 5 calories per gramme. So it is helpful in many conditions of impaired nutrition. But it is not superior to fats and carbohydrates, because, *firstly* the rate of combustion of alcohol is fixed and is not substantially increased by exercise and *secondly*, fats and sugars taken in excess of the immediate need are stored in the body. But if alcohol happens to be beyond the limit oxidation, produces its poisonous action on various tissues through which it circulates and is not stored any where.

Recently alcohol (95%) 60 ml. with 5% of each of aminoacids and glucose in 1000 ml. of fluid very slowly intravenously taking 4 hours, has been found a suitable post-operative nutrition in patients unable to take food orally : this may be repeated 8 hourly or with a longer interval. (Rice, Orr and Enquist, 1950)

(b) LIVER.—From the stomach and duodenum, the absorbed alcohol passes direct into the liver through the portal circulation. It is probably **oxidised** here along with oxidation of glucose. It is been found that increased glucose utilisation by insulin injection increases the rapidity of oxidation of alcohol also (Goldfarb, Bowman and Parker). An alcoholic intoxication is thus quickly recovered from by using glucose and insulin. Alcohol in small amount, is so much diluted in the portal blood stream and readily disappears that it does not cause any injurious effect. But if the quantity is large, it **irritates the liver parenchyma** resulting in acute hepatitis. This subsides in a few days but if such big doses are frequently repeated, the liver may undergo progressive fatty degeneration and fibrosis.

(c) PANCREATIC and BILIARY SECRETIONS are also increased : this is probably due to the increased formation of secretin by the action of acid chyme on the duodenal mucous membrane, which carried into the blood, acts as a hormone to both the liver and the pancreas, **stimulating their secretions**.

(b) CIRCULATION.—Alcohol is believed to be a circulatory stimulant. As soon as it is taken, it gives a feeling of exhilaration and warmth. But careful experiments have conclusively shown that alcohol in therapeutic doses, has no direct action on the heart muscle and in large doses it is depressant and consequently injurious. Its actions on the cardiovascular system may be summed up as follows.

(i) Reflex or immediate action when taken orally.

- (ii) Action on the blood vessels.
- (iii) Action on the nutrition of the heart muscles.

Reflex or immediate action.—As soon as alcohol reaches the mucous membrane of the mouth and stomach in a fairly concentrated form, owing to local irritation of the afferent nerve-endings, it **reflexly stimulates** the cardiac accelerator mechanism and the heart beats faster and more forcibly [and alcohol is often used as a restorative in a case of syncope³¹⁴]. This quickened heart beat continues nearly all throughout the stage of excitement of narcosis. But if a very big dose is taken, the heart is distinctly slowed from stimulation of the vagal centre (cardiac inhibition).

After absorption.—Its first action is **dilatation of the blood vessels** of the skin and slight constriction of the splanchnic vessels. There is flushing of the skin, especially of the face, and a general feeling of warmth. The circulation is therefore **accelerated without any rise of the blood pressure**, although in many cases during the stage of excitement a slight rise of blood pressure is common. This vaso-dilatation is partly due to depressant action of alcohol on the **vaso-constricting** (vaso-motor) centre and partly to the gastric cardio-acceleratory reflex. On the skin, vaso-dilatation acts as a mild **diaphoretic**. A dose of alcohol is useful when one is at home in a warm room after an exposure to chill and fatigue.

In fevers, alcohol is a mild **antipyretic**. This is due to the same vasodilating action, favouring a greater radiation of the raised body-heat from the skin and to a slight extent, to its depressing the heat regulating centre. But if much excitement with muscular movements is present, temperature may even slightly go up.

A large group of observers thinks that alcohol has no definite beneficial action on the circulation. Others believe that in small doses, in a previously weakened heart which has worked for some time without sufficient nourishment it somewhat increases the force of contractions and is useful. [It is therefore often given in pneumonia but it mainly **acts as food**, not only for tissues in general but also directly for the heart]. There is a certain amount of dilatation of the coronary arteries which may be an advantage for the nourishment of the heart. The pulse rate often comes down probably due to the sedative action of alcohol on the central nervous system, diminishing the bodily movement, [For the same reason, it is also largely prescribed to a woman after child birth or

(314) R

Sp. Ammon. Aromat. min. 20

Sp. Chlorof. min. 15

Aq. Menth. Pip. ad. fl. oz. 1

Mix. A quick restorative in syncope.

during convalescence from a prolonged illness, alcohol acting as a restorative].

But this beneficial action is not to be seen if alcohol is taken in large amount causing a blood concentration reaching nearly 0.4%. Its only action then, is one of **circulatory depression**, without any stage of stimulation at all. By its action on the heart muscles, first on the auricles and then on the ventricles, and on the vaso-motor centre, the heart beat become weak and the blood pressure falls. A very large dose may cause immediate death by reflex inhibitory action on the heart from the stomach through the vagal mechanism.

(e) **RESPIRATION** is moderately **accelerated**: probably this is a reflex action from the excitement but is also partly due to increased oxygen intake for the increased metabolism. Alcohol has no action on the respiratory centre except with a poisonous dose causing fatal depression.

(f) **NERVOUS SYSTEM**.—Alcohol is mostly taken for its **exhilarant** action on the nervous system. It has a certain amount of chemical affinity to collect in the brain lipoid in preference to other tissues. Therefore it shows its specific action there in comparatively smaller doses than elsewhere. (See p. 455).

In small doses, alcohol usually produces a sensation of mental and physical well-being and a contented benevolent and communicative state of mind. This is the stage of **euphoria**. If the dose is increased, a certain amount of **psychical instability** develops which is shown by talkativeness even in persons otherwise reserve. If a speech is made, it is with less hesitation and greater fluency because of less thinking before speaking and less concern about the niceties of expression or the kind of impression likely to be made on the audience.

At this stage, the head feels hot, the face is congested, the carotids throb and the pulsation in the temporals may be visible. There is often a tendency to commit impulsive and unpremeditated acts.

If the dose is increased further, acute alcohol poisoning rapidly ensues. The mental balance is completely lost and all kinds of inconsiderate actions are performed. The gait becomes unsteady, the utterance is indistinct and incoherent and the previous animation gives place to drowsiness and inclination to sleep. Nausea and vomiting frequently make their appearance and the flush of the face is replaced by pallor.

This stage of excitement shows marked individual peculiarities. In some, this is fairly prolonged and in others the stage of deeper narcosis and sleep quickly follows.

With very large doses, its action resembles ether and chloroform anæsthesia. There is **complete insensibility** and narcosis

with loss of reflex also muscular relaxation, soft pulse, lowered temperature, stertorous breathing, cyanosis and finally death from respiratory failure.

The intensity of narcosis for the quantity taken is variable. An addict can stand a bigger dose but a person unaccustomed may feel exhilaration even with one ounce. A concentration of alcohol in the blood between 0.025 to 0.1% causes euphoria : over 0.12%, symptoms of drunkenness, over 0.27% deep narcosis and over 0.7%, death.

A special chemical test of the blood is performed for medicolegal purpose to determine the intensity of intoxication. A blood concentration of 0.2%, urinary excretion of 0.2% and exhaled air concentration of 1 mg. per litre are accepted in law courts as a *state of definite intoxication*.

The actions of alcohol in successive stages were formerly believed to be due to initial stimulation of the different parts of the nervous system from the highest to the lowest, followed by their paralysis (Binz.).

Schmiedeberg has established the present doctrine that, from the beginning, the only action of alcohol is one of pure narcosis and that, the **stimulation is only apparent**, being due to paralysis of the superior psychic functions which normally play a controlling part and maintain a restraint on the behaviour of the individual in everyday life.

It has been found that anything requiring greater intellectual power, skill and attention is done better and more correctly without alcohol than with it and the same may be said about the capacity for muscular exertion and power of endurance. The power of resisting infections may be lowered.

The action of alcohol is, however, one of **universal depression** and the centre that is highest in evolution is affected first. This depression follows the inverse order of development and lastly the most primitive centres, namely those for the vital functions of the body (respiration and circulation), in the medulla are affected. This is called the **Law of Dissolution**. Thus, first the highest **cerebral centre** is affected, namely, the intellectual centres, then the lower cerebral centres, motor and sensory, emotional and animal. Then follow the **cerebellum** and **basal ganglia** (shown by reeling, unsteady gait and automatic movements) : the **spinal centres**, shown by profound muscular relaxation, lowering of reflex functions, analgesia and involuntary passing of urine and faeces ; and lastly the vital centres in the **medulla**, are depressed, resulting in the failure of respiration and circulation and death.

Alcohol 95% one part with glucose 5% two parts has been slowly administered intravenously for 15 to 20 minutes. Often after 40 to 60 c.c. of alcohol injection sleep starts which develop into **deep anæsthesia**. Sleep lasts for 3 to 5 hours. But on recovery sometimes mental symptoms may appear. So this is not suitable for general anæsthesia.

Alcohol in some cases causes increased secretion of the *cerebrospinal fluid*, thus increasing the subarachnoidal fluid pressure : may also cause cerebral oedema.

Alcohol has no direct action on the peripheral nerves : these may however be affected in long-standing chronic alcoholism. In such cases, on account of deficiency of aneurine intake, signs of **peripheral neuritis with myocardial dilatation** appear.

(g) **EXCRETION.**—In moderate doses as 1 to 2 ounces, alcohol is mostly oxidised amounting to over 90% and only small amount is excreted through the lungs and the kidneys. The kidney elimination is about 1 to 2% and acts as a mild **diuretic**. But if taken in bigger doses and this is frequently repeated, it causes, as in the liver, fatty and fibroid changes in the kidneys.

TOLERANCE FOR ALCOHOL.—People accustomed to take alcohol frequently develop a sort of tolerance (although not as much as with morphine and nicotine) so that they can oxidise a larger amount and the cerebral centres also can resist a larger dose. There is consequently, a great risk of immoderation and formation of habit.

But the mucous membrane of the *stomach, pharynx and larynx* and the *liver* tissue do not acquire such tolerance. As the alcoholic habit is continued, these progressively degenerate leading to gastritis and fatty changes. Further effects of chronic alcoholism are a *general devitalising action* upon all the tissues of the body. The will power, moral sense and mental capacity are progressively impaired. Tremor and rarely convulsions may be seen. The general impairment of the tissues is shown by lowered resistance to bacterial infection : this happens even with a moderate dose of alcohol taken repeatedly fairly long. If an alcoholic gets pneumonia, he has a bad time.

Chronic alcoholism is believed to have injurious action on the reproductive organs and often leads to sterility.

As after effect, peripheral neuritis (diminished vitamin B₁ absorption), delirium tremens and even insanity may be seen.

SUMMARY.—(i) Alcohol is a **solvent** and largely used in pharmacy. It is a *preservative* also.

(ii) *Externally*, it is in 25 to 30% solution a *cooling* application used for bruises, various kinds of superficial inflammation and for febrile conditions mostly used as Eau-de-Cologne. In 50% solution, it **hardens the skin** of the pressure-spots of bed-ridden patients. In 70% solution it is a powerful *antiseptic*.

(iii) *Internally*.—(a) As a **stomachic-digestive**, it is largely used as 10 to 15% weak wines, often combined with aromatics and bitters, during convalescence and for people in a low state of health.

(b) In fevers, as an **antipyretic**, a food and a hypnotic, it is fairly popular. Patients with nephritis stand alcohol badly.

Old cognac brandy is usually preferred and a dose of 2 fluid oz. need not be exceeded in 24 hours.

(c) As a quick **restorative**, brandy, 30 to 60 minims in 1 fluid oz. of water is frequently given in fainting attacks.

(d) In a healthy person, alcohol is occasionally indicated to act as **restorative** by removing the sense of fatigue of prolonged muscular exertion and helps greatly to give rest and sleep. But great care should be taken to avoid formation of habit.

(e) Alcohol, 5 to 7% 50 c.c. is used as a **test meal** for estimating the gastric acidity.

SPIRITUS METHYLATUS INDUSTRIALIS

(Sp. Meth. Indust.), Industrial Methylated Spirit

METHYLATED SPIRIT contains in 19 volumes of alcohol 95%, 1 volume of approved wood naphtha and is similar to 66 O.P. Industrial Methylated Spirits. If 74 O.P., it is called ABSOLUTE INDUSTRIAL METHYLATED SPIRITS.

This is a commercial product and is used for *burning purposes*, for *external application* and as *solvent* in various trades and industries.

THERAPEUTICALLY, it is used mainly *externally* in liniments but is unsuitable for *internal* administration.

Non-official Preparations

METHYL ALCOHOL, CH_3OH , is known in commerce as wood naphtha or wood spirit and contains acetone and other impurities. It is toxic and causes nausea, vomiting, abdominal pain, a sense of exhaustion and delirium passing on to prolonged coma. The cumulative effect is optic neuritis. In pure form, it is a solvent, used in the preparation of microscopic stains.

ISOPROPYL ALCOHOL and PROPYLENE GLYCOL are used in pharmaceuticals as *solvent* for alkaloids, volatile oils, steroids and natural and synthetic dyes : also used in arts and in perfumery and cosmetics.

PROPYL GALLATE is *antioxidant* and is used to prevent auto-oxidation of fixed oils and fat (0.2% of it prevents rancidity, often used in cocoa-nut oil toilet products) also used for the same purpose in ether and in paraldehyde.

II. ANÆSTHETICS

The anæsthetics are drugs employed for abolishing the perception of all external afferent stimuli. (a) This loss of *sensation* may involve the **whole body** including the loss of *consciousness* along with *muscular relaxation* or (b) it may be of a **localised nature**, general consciousness being unimpaired.

The former is called a **general** and the latter, a **local anæsthetic**. In either case, the object is to perform some surgical operations painlessly. Further, the general anæsthetic prevents anxiety and fear during the operation.

General Anaesthetics

The first general anæsthetic discovered was *nitrous oxide* by Priestly in 1776 but was not used for many years. Long in 1842 found that *ether* was a general anæsthetic. Morton in 1846 more elaborately demonstrated its efficiency. Simpson in 1874 introduced *chloroform*.

The main object is to *paralyse only the sensory area* of the cortex but no drug has such a limited and selective action and therefore drugs of this group, when administered either by the mouth, inhalation, intravenous injection or per rectum causes total unconsciousness associated with insensibility to pain. There is, to start with, paralysis of the superior psychic

functions and this is followed by inhibition of the sensory, motor and the reflex functions.

If the anæsthetic is pushed any further, the medullary centres are affected. The cardiac and respiratory paralysis follows, ending in death.

An ideal anæsthetic should therefore be capable of (i) easy administration, (ii) produce effect rapidly which should also (iii) pass off as rapidly, (iv) cause sensory paralysis and muscular relaxation, (v) have a wide margin of safety, the dose causing anæsthesia being not sufficient to affect the medullary centres and (vi) leave no after-effects.

Unfortunately no drug yet known fully satisfy all these items and the choice falls on those that satisfy the most.

MODE OF ACTION.—It is not definitely known how these anæsthetics act. (i) Their special affinity for the nervous tissues is at least partly due to their greater solubility in the brain lipids than in the watery plasma of other tissues. (Meyer and Overton).

The oil and water *co-efficient of partition* is exemplified by alcohols. Lipid soluble properties progressively increase starting from methyl, ethyl, propyl, butyl and amyl alcohols and so also their narcotic power. But if the hydroxyl groups are increased as in ethyl alcohol, glycol and glycerin, co-efficient of partition between lipid and water falls with lessening of narcotic properties.

The objection against this theory is that the narcotic properties of dissimilar substances as alcohol, acetone and chloral hydrate are not in proportion to their lipid solubility. Their relative solubility has the ratio of 1, 2 and 6 but narcotic property is 1, 16 and 1. Further, other anæsthetics as alkaloids or inorganic ions do not comply with this theory.

Other probable theories are: (ii) Clark thinks that the narcotics act by adsorption so that a layer of $\text{CH}_3\text{—CH}_2$ group is interposed between the active surface and water outside, thus forming a barrier to molecular interchange. Biological action of narcotics bears an obvious relation to this power of lowering of surface tension. (iii) Traube (1913, 1915) thinks, narcosis is related to disturbances in surface tension which allows the drug to accumulate on the cell surface. (iv) Quastel (1932) opines that these act by interfering with enzymic components of the respiratory system of the nerve cell and inhibition of oxidation of glucose, sodium lactate and sodium pyruvate by the brain tissue and consequently lowering its functional activities. Or (v) anæsthesia may be due to decreased negative potential of the cerebral cortex and lessened electrical conductivity through the cerebro-spinal system (Burge, 1936: Forbes and Morison, 1939).

Taking into consideration the different cases, solubility in brain lipid and adsorption on the surface of the cells appear to be the main items determining the various phenomena of narcosis.

ANÆSTHETICS IN COMMON USE

(i) The **volatile anæsthetics** are given by *inhalation* so that anæsthesia is readily induced and it disappears also equally readily when further administration is stopped. This group includes Chloroform, Ether, Nitrous oxide, Ethyl chloride Ethylene, Cyclopropane, Divinyl ether and Trichloroethylene.

ETHYL BROMIDE, ETHANOL (a mixture of ether 95% and butyl alcohol 4%) and SOMNOFORM are sometimes used by inhalation.

Ethyl alcohol, Methyl alcohol, Acetone, Benzol and Benzene have somewhat similar action. But none of these abolishes the pain sense completely, except in doses that cause dangerous depression of the medullary centres and are therefore not used for this purpose.

(ii) But with others, administered either *per rectum* or by *injection*, anæsthesia is of longer duration. Here the main object is to cause preliminary partial anæsthesia (**basal anæsthesia**) which is intensified by one of the volatile anæsthetics. This include bromethol and paraldehyde *per rectum*, scopolamine-morphine subcutaneously: soluble hexobarbitone, pentobarbitone, phenobarbitone and thiopentone and a few other barbiturates intravenously.

CHLOROFORMUM (*Chlorof.*), CHCl_3

Chloroform is trichloromethane with 1 to 2% by volume of dehydrated alcohol and is prepared from ethyl alcohol or acetone by heating with chlorinated lime, slaked lime and distilled water and subsequent purification. It is a colourless, volatile liquid with a peculiar sweetish burning taste and sweetish smell. It is non-inflammable.

It is soluble at 15.5° in 200 parts of water and freely so in dehydrated alcohol, oils, solvent ether and most organic solvents.

It *decomposes* in the presence of light and air and so should be stocked in an amber-coloured bottle which should be filled up completely so as not to leave any air spaces.

It must not redden blue litmus paper, nor alter with silver nitrate (cloudy), with H_2SO_4 (yellowish), with cadmium iodide and starch (bluish).

Dose, 1 to 5 minims or 0.06 to 0.3 ml.

OFFICIAL PREPARATIONS.—(i) **Aqua Chloroformi** (*Aq. Chlorof.*), See p. 37 or one minim of chloroform in 400 minims of distilled water. Dissolve by shaking. Dose, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. (ii) **Emulsio Chloroformi** (*Emuls. Chlorof.*), See p. 38. Dose, 5 to 30 minims or 0.3 to 2 ml. (iii) **Spiritus Chloroformi** (*Sp. Chlorof.*), Chloric Ether. See p. 54. Dose, 5 to 30 minims or 0.3 to 2 ml.

Non-official Preparation

TINCTURA CHLOROFORMI ET MORPHINÆ Co., a substitute for *Chlorodyne*.—Chloroform 75, tincture of capsicum 25, tincture of Indian hemp 100, oil of peppermint 2, glycerin 250, morphine hydrochloride 10, dilute hydrocyanic acid 50 and alcohol (90%) q.s. to 1000. (Strength $\frac{3}{4}$ min. chloroform, $\frac{1}{2}$ min. acid hydrocyanic dil. and $\frac{1}{11}$ gr. of morphine hydrochloride in 10 min. Dose, 5 to 15 minims or 0.3 to 1 ml.

Pharmacology [and Therapeutics]

Chloroform is mainly used by inhalation for inducing general anæsthesia for surgical operation. Although first prepared in 1831 it was introduced in practice for this purpose several years after by Simpson in 1874. In fact, it may be said that, for rapid advance of surgery chloroform is as much responsible as the knowledge of antiseptis and asepsis introduced by Lord Lister (1867).

On account of its greater toxicity, chloroform is now not as frequently used singly for prolonged anæsthesia in a major operation.

APPLIED EXTERNALLY, it has the same action as alcohol but is much more powerful. Thus, if allowed to evaporate from skin surface, chloroform constricts the superficial blood-vessels and induces slight local anæsthesia. But if the evaporation is prevented, it acts as a **rubefacient**^{3 15} and if applied for some time, it may cause vesication. It is a **preservative** of an aqueous extract of vegetable and animal products : one minim per ounce may do.

TAKEN INTERNALLY.—In undiluted form, chloroform irritates the mucous membranes. In the *mouth*, it gives hot **burning sensation**. In dilute solution, it has a **sweetish taste** and reflexly increases the **salivary secretion**. On the *stomach* and the *intestine*, the same action continues increasing the gastro-intestinal secretions and movements. It is therefore a **stomachic** and **carminative**^{3 16}. [Hence the spirit or emulsion of chloroform or chloroform water is used as a flavouring and carminative in many mixtures]. It is combined with other diffusible stimulants for **reflexly augmenting** the action of the heart, (the gastric reflex, on the cardioacceleratory centre. (See p. 447). In one minim dose, it is a **gastric sedative** controlling vomiting.

NERVOUS SYSTEM.—But its chief action is as a **general anæsthetic**. Given by inhalation, it is quickly absorbed into the circulation about 90% taken up by red blood corpuscles and about 10% gets into the plasma, and produces its selective action on the brain cells. Chloroform gradually accumulates in the brain and other nerve tissue cells. The condition that follows in successive stages has been divided as follows : (i) disorganised consciousness and analgesia, (ii) excitement and delirium, (iii) surgical anæsthesia and (iv) bulbar paralysis.

(315) R
 Menthol
 Chloralls Hydras
 Camphora
 Chlorof. equal part (Lucus)
 For neuralgia and sciatica.

(316) R
 Sp. Ammon. Aromat. min. 20
 Sp. Chlorof. min. 15
 Sp. Cinnam. min. 20
 Aq. Camph. ad. fl. oz. 1
 A carminative and stimulant.

STAGES OF CHLOROFORM ANÆSTHESIA

| Stage | Respiration | Colour of face | Muscular relaxation | Pupil | Eye ball movement | Eye reflex | Pulse rate | Blood pressure | Temperature | Surgical Operation |
|--|------------------------------|------------------------------|---------------------|--------------|-------------------|------------|-----------------|----------------|-----------------|---|
| Stage I <i>Analgesia</i> | Thorac. Abd. | Flushed | Nil | Normal | Voluntary | Normal | ++ | + | Normal | Labour 1st stage: Normal Labour. |
| Stage II <i>Delirium</i> | Thorac. Abd. irregular | More flushed | Decreased | Dilated | +++ | Present | +++ | ++ | Slightly raised | Nil |
| Stage III <i>Anæsthesia</i> PLANE 1 | Thorac. Abd. deep | Flushed with ether, cyanosed | Moderate | Small | +++ | Lost | Normal | Normal | Normal | Thoracic, Obstetric, Thyroid, Brain, Bone, Eye, Nose, Bladder, Urethra. |
| PLANE 2 | Abd. Thorac. deep | Flushed | Complete | Small | Fixed | Lost | " | " | Slight fall | Throat, Joint, Abdomen, Rectum. |
| PLANE 3 | Abd. feeble | Flushed | Complete | Bigger | Fixed convergent | Lost | Fast | Falling | Falling | Some abdomen. surgery: obstetrical version. |
| PLANE 4 | Abd. very feeble | Cyanosed | Faccid | Dilated | Fixed | Lost | Fast and feeble | Falling | Falling | — |
| Stage IV <i>Medullary Paralysis</i> | None | Pallor | Paralysis | Much dilated | Fixed | Lost | Not felt | Very low | Low | — |

THE FIRST or the stage of **Disorganised Consciousness and Analgesia**.—The effects to commence with are due to the *local irritation* on the different mucous membranes and the reflex action arising therefrom. The heavy vapour falls from the mask upon the face and causes various local effects. From the *eyes* tears flow : in the *mouth* and *throat* is felt pungent sweet taste of chloroform causing cough and flow of saliva. The *nasal mucous membrane* is also irritated giving rise to a sense of suffocation and by a reflex impulse working through the trigeminal nerve, and also through the vagal ending in the larynx and bronchi, the respiration becomes slow and shallow or may even entirely cease. This preliminary stoppage is a reflex act and is not to be confounded with the paralysis of the respiratory centre of the last stage of narcosis. From the same reflex, the heart is also slowed. If fresh air is now allowed, the respiration once more begins. The vapour passes down the bronchial tubes and irritates the sensory nerve endings of the vagus. A new reflex now appears : the respiration quickens and this accelerates narcosis. The *pulse rate* and *blood pressure* may be moderately raised and *respiration* is slightly quickened or made irregular mainly from excitement.

A feeling of *warmth* is diffused throughout the body and soon the limbs feel heavy and helpless. *Consciousness* is dimmed and although the muscles are not yet relaxed, *analgesia* is already established.

THE SECOND or the stage of **excitement** (delirium) now begins. A dreamy state ensues. Hallucinations alternate in the mind, sometimes cheerful and sometimes sad. The patient laughs and sings or has an indistinct idea that he is in danger and gives vent to his uneasiness by screaming and violent movements of the body. The condition resembles the excitement of drunkenness. He is best quietened in this stage by gentle restraint while much rough handling makes him all the more violent.

The *face* becomes flushed, the *skin* is warm and moist and on account of struggling, the *pulse* is often quickened, *blood pressure* slightly raised and the *respiration* is irregular. There may be occasional inspiratory or expiratory arrest, coughing or alternate periods of shallow and deep breathing. The *pupil* which was so long dilated, probably from the excitement, towards the end of this stage begins to contract. The *eyeballs* rhythmically oscillates often in a lateral direction. *Vomiting* sometimes takes place especially if the patient had anything to eat recently : this is to some extent due to local irritation of the vapour on the mucous membrane of the stomach but mainly from central action, due to the stimulation of the vomiting centre in the medulla. Towards the end of this stage *muscular relaxation* begins.

This period of restlessness is sometimes called the *Stimulation Stage*. But in fact there is no stimulation at all. This is

really due to narcosis of the superior cerebral centres and so the lower motorial ones, being uncontrolled, show irregular and disorganised activity.

Owing to stronger narcotic property and more rapid absorption of chloroform, this stage of excitement is very much shorter than that of alcohol narcosis.

This "stimulation" of the excitement stage is again of a very varied *intensity* and *duration*. In children and in delicate persons, it is comparatively slight and brief, but is usually much more violent and lengthy in persons addicted to alcohol. The latter may scream and even behave like a maniac for a quarter of an hour before he is quietened and there is a chance of this condition passing straight into the last stage of paralytic narcosis. The reason is this : (a) these people are habituated to alcohol, a narcotic that is akin to chloroform for which the cerebral centres have gained a certain amount of tolerance. So these centres may not be narcotised till a dose is taken sufficient to inhibit the medullary function leading to sudden death.

(b) Another important cause of sudden death in the alcoholics is heart failure. It has already been pointed out that alcohol causes degenerative changes in the heart muscles if continued in toxic doses for a long time. So these people may have already a weak heart which fails under profound narcosis, when a high concentration of chloroform is reached in the coronary circulation.

THE THIRD STAGE : Stage of Surgical anæsthesia.—This stage is divided into four planes (Guedel 1937). These are

Plane 1.—The face is flushed. Pupils are slightly contracted, conjunctival reflexes lost, eye ball movement gradually lessens, respiration is regular and full and movements are both abdominal and thoracic. Muscular relaxation is partial and pulse and respiration are normal.

Plane 2.—The eye balls are fixed : all superficial reflexes are lost : muscular relaxation is complete. Pulse, respiration, blood pressure and the pupils are as in plane 1.

These two planes are suitable for most of the major operations.

Plane 3.—Respiration is more abdominal and less thoracic. All reflexes are lost. Pupils have commenced dilating. Pulse is quicker and blood pressure falls.

Plane 4.—Face is flushed and cyanosed. Respiration is very feeble or stopped, pulse is also very feeble, almost absent. Pupils are widely dilated and the patient is in a stage of profound shock.

The *temperature* gradually falls and markedly in the plane 4.

Thus with continued inhalation, the **reflexes** are completely abolished, so that touching of the cornea no longer causes the

reflex closure of the eye-lids. All **voluntary muscles** are relaxed. The back and the extremities are first affected, then the genitals and the rectal sphincter and the muscles of mastication are relaxed last of all, so that the teeth may be clenched when all the other muscles are relaxed. Therefore, for operations in the mouth, profound anæsthesia is required and if proper care is not taken, it may go up to narcosis of the medullary centres.

Although even before the loss of reflexes, there is loss of sense of pain (**analgesia**), sensory paralysis preceding the motor, it is necessary for surgical operations to wait till motor relaxation and the loss of reflexes are complete. Otherwise the afferent impulses from the surgical cut are not totally shut off and there may be reflex stoppage of the heart in consequence.

When the stage of relaxation is attained, the patient is in a fit state for operation. An elaborate and painful surgical work can now be performed without any distress and much of the marvels of modern surgery is due to this wonderful analgesic property of the volatile anæsthetics.

In plane 1, thoracic surgery, obstetrical, thyroid, brain, eye, nose, urethra and bone : in the plane 2, throat, joints and rectum and most of the abdominal surgeries are performed : in plane 3, some abdominal surgery may be done with care and obstetric versions : and one should never go beyond.

That complete analgesia develops earlier than complete anæsthesia, is evident when an operation is performed before full anæsthesia, the patient being still restless or even shouting. When he regains consciousness, he does not remember to have felt any pain during the operation.

During this stage of deep narcosis, important changes in the **pupil** take place. It was dilated in the second stage but it now contracts and remains contracted so long as the patient is maintained in this stage. Dilatation of the pupil only occurs if either the patient is not fully narcotised or is in a condition of deeper narcosis than is safe. So it is very important to **watch the condition of the pupil during the whole period of anæsthesia**.

Pupillary constriction in stage III is due to abolition of cerebral impulses which control and inhibit the tone of oculomotor (pupil-constricting) centre (*Edinger, Westphal nucleus*).

Preanæsthetic medication by morphine-scopolamine and a barbiturate tends to constrict the pupils moderately.

The *eye balls* move about in the earlier stage but becomes fixed at the stage of full anæsthesia.

The **pulse** continues to be slow and regular although a little soft, but becomes quicker when the fourth plane is neared. The **respiration** is abdomino-thoracic and somewhat slow and regular but deep and may even be stertorous, owing to paresis of the soft palate and falling back of the tongue through relaxation of the pharyngeal and lingual muscles. With deeper

anæsthesia, it is more abdominal and of low amplitude which finally stops at the fourth stage.

The normal contractility of the **unstriated muscle fibres** as of the stomach and intestines is slightly lessened and even after the anæsthesia is stopped, it takes some hours to recover (Miller).

If the patient is in labour, with moderate anæsthesia the uterine contractions are not much affected. But if deep, these are enfeebled. This is probably due to direct action on the muscles and not through the central nervous system. For prolonged anæsthesia in such cases, ether should be used : with chloroform, such a quantity may pass into the foetal circulation as to cause death of the foetus although not affecting the mother and this should be kept in mind.

THE FOURTH STAGE or STAGE OF Bulbar Paralysis.—When the narcosis has gone beyond the fourth plane in the third stage, in addition to nervous influence, chloroform directly depresses the muscle fibres of the heart, blood-vessels and of the different sphincters. The heart contracts feebly, the auricles being more affected than the ventricles. the blood pressure falls and the bladder and the rectum are automatically emptied. The respiratory centre is no longer supplied with an adequate quantity of blood and this combined with direct depression of it, cause the respiratory movements more and more shallow, irregular and slow. The skin and the mucous membranes become cyanotic and the pupils are dilated. If proceeded further, the pulse becomes very feeble, of low pressure and intermittent and finally imperceptible. The medulla being paralysed death takes place from either **respiratory or cardiac failure**.

Thus except for the rapidity of action, there is a close resemblance between alcohol and chloroform narcosis. There is the same descending depression and paralysis, starting from the superior psychic centre to the medulla in the end, the depression primarily involving the sensory or afferent tracts and afterwards of the motor neurones.

In addition to cause surgical anæsthesia, chloroform inhalation may with advantage be resorted to (a) to *relieve convulsive movements* of condition like tetanus, strychnine poisoning, uræmia and intracranial conditions ; (b) to *cause muscular relaxation* as for reducing a fracture-dislocation or for physical examination of the abdominal viscera in a hyperexcitable person : (c) to *relieve* biliary, intestinal or renal *colic*. Here only a lighter degree of anæsthesia is only aimed at.

ABSORPTION AND EXCRETION.—If further inhalation is stopped in the third stage, most of the anæsthetic is rapidly eliminated through the lungs in the expired air and the sequence of events described above is rapidly repeated in the reverse order. Muscular tone, reflexes and sense of pain.

reappear and with a brief period of excitement, the patient quickly recovers so much so that in a short time, he may be able to respond when talked to. After a brief conscious period, he often falls asleep but this is quite harmless and it is better that he should be allowed that period of rest.

In the earlier stages of administration, a volatile anæsthetic from the lung alveoli passes into the pulmonary circulation and therefrom to the arterial system and through the capillaries into the tissues which in the earlier stage of anæsthesia take up the most. In its passage through the tissues into the venous system, in the beginning, the anæsthetic is in greater concentration in the arterial than in the venous blood as a certain amount of it is absorbed by the tissues as it passes through the capillaries. As further administration is continued and stage of full anæsthesia is reached especially if it is prolonged, the arteries and the veins contain it in nearly equal concentration. But when the anæsthetic is stopped, it is in greater concentration in the venous circulation on its way towards elimination through the lungs. Both absorption and elimination of the anæsthetic are fairly rapid.

The concentration of it in the blood necessary for complete surgical anæsthesia is about half of what is fatal ; therefore the margin of safety is not very great.

CIRCULATION.—Chloroform in higher concentration in the blood is a *cardio-vascular poison* acting directly on the auricles and with a bigger dose on the ventricles also and finally the heart stops in diastole.

The *vasomotor centre* is depressed causing peripheral vaso-dilatation. This is more marked on the splanchnic blood vessels, the effect being partly due to direct action on the musculature of the blood vessels.

TEMPERATURE falls during anæsthesia. This is partly due to vaso-dilatation favouring increased diffusion through the skin but mainly from diminished heat production on account of lessened muscular activity and paresis of the heat regulating centre in the hypothalamus. This fall may be 1.5 to 2°C . Therefore the patient should be kept well covered during the whole period of anæsthesia.

METABOLISM is seriously affected by chloroform. It is a tissue-poison and if inhaled sufficiently long, it causes *fatty degeneration* of the *liver*, *kidneys* and of the *heart muscles*. Nitrogen and unoxidised sulphur are increased in the urine showing *increased tissue destruction* and disturbed oxidation. *Carbohydrate metabolism* is also altered : acetone and glycuronic acid appear in the urine. The blood sugar level rises and the glycogen content of the liver gets markedly reduced. Chloroform is therefore rather unsafe in diabetes mellitus.

Some persons feel perfectly all right after regaining consciousness from anæsthesia. But a large number, however, suffer from various **after effects** for some time, such as a feeling

of general *weakness*, inability for any mental effort, *headache* and *vomiting*. The last may be very troublesome and in some cases persistent. This condition is due to the action of the narcotic on the vomiting centre as well as locally on the stomach where it is excreted and further aggravated by a certain amount of *ketosis* which is sometimes superimposed.

In some cases, *gastro-intestinal atony* develops, rarely even acute dilatation of the stomach. Previous administration of morphine tends to counteract this tendency.

The urine sometimes takes a yellow colour, may be due to bile pigment and in some cases there may be temporary albuminuria and the urinary quantity diminished. The cause is uncertain. But there is no doubt that chloroform in some cases is deleterious to the kidneys and may induce typical fatty degeneration.

DEATH DURING ANÆSTHESIA

Chloroform is a powerful cardio-vascular poison and in most cases fatality follows from *circulatory failure*.

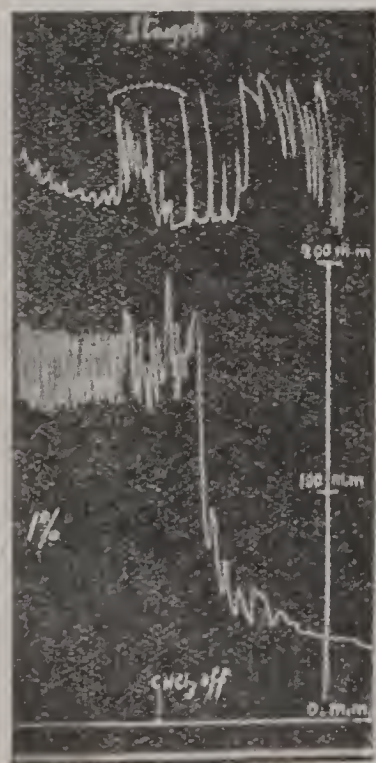


Fig. 23.—The upper curve is of respiration and the lower, of blood pressure of a cat under chloroform. Violent struggle is immediately followed by ventricular fibrillation, the blood pressure rapidly falls and the respiration becomes gasping till finally stopped. (Levy).

Death may occur at any stage of chloroform anæsthesia and in various ways. These are usually as follows :

(i) In the *first stage*, often after a very short period of inhalation, the patient suddenly becomes markedly blue, the radial pulse disappears, all the muscles are relaxed, the heart stops in diastole and after 2 or 3 short inspirations, death supervenes. This is due to **reflex stoppage** of the heart, from excitation of the vagal centre, caused by the irritant action of overconcentrated chloroform on the mucous membrane of the nose. A normal heart reacts to such a reflex with merely a slow pulse or at most, a stoppage for few seconds and starts again as soon as fresh air is allowed. But if the heart is already weak, this stoppage may lead to fatality. So it is important to administer chloroform in the beginning well diluted with air.

An injection of atropine sulphate which paralyzes the vagal endings is often a helpful preliminary measure.

(ii) In some rare cases, during the stage of light surgical anæsthesia in a patient with pupils contracted,

in the *second stage*, even

breathing well and has a good pulse, suddenly dangerous symptoms may appear. Pulse becomes feeble and is soon imperceptible; the respiration at first becomes laboured and then ceases and death takes place,—believed to be due to **ventricular fibrillation**.*

In many cases, during this stage, irregularity of cardiac rhythm is common. Hill (1932) found extrasystoles of diverse origin in the electrocardiogram.

(iii) If chloroform is *given in a concentrated form* for inducing rapid anæsthesia, owing to increased vascularity, the cerebral circulation gets it in much greater concentration than the rest of the body and the respiration may fail. Further inhalation being stopped, extra amount is passed out of the cerebral circulation rapidly and the respiration is spontaneously re-established.

If the patient had morphine as a preanæsthetic narcotic, respiratory centre may be so depressed that it may fail under chloroform.

A child crying and struggling during the stage of induction may from hyperpnœa lose much CO_2 : this lowers the threshold of the respiratory centre which may fail during chloroform anæsthesia.

In some of these cases, a large amount of chloroform may get into the coronary circulation and cause death although the concentration in the venous blood is still comparatively low.

(iv) Death occurs more frequently during *deep anæsthesia beyond the third plane* and it is due to **paralysis** either of the **respiration** or of the **circulation** and most frequently of the latter. In many cases, this failure takes place so simultaneously that it is difficult to decide which stops first. It is therefore equally important to watch the conditions of the **pulse**, **respiration** and the **pupils** during the whole period of deep anæsthesia.

COMPLICATIONS.—(i) *Delayed chloroform poisoning* occasionally causes death, many hours or even several days after the narcosis proper has ended. by progressively increasing the depression of the circulation ending in collapse and death. This may be the immediate effect of narcosis or the patient may wake up for a time and then fall asleep into coma. The pulse becomes feeble, the urine exhibits products of protein

* The exact mechanism is still unknown. It is believed to be increased excitation of the heart through the sympathetics by sensory impulses during light anæsthesia or to increased secretion of adrenaline acting on the accelerator apparatus during struggle (Levy). So adrenaline injection should not be given in such cases. The vagal inhibition is therefore, found among the vagotoniacs and ventricular fibrillation in the sympatheticoniacs.

destruction and also acetone. The post-mortem examination shows an advanced fatty degeneration of the heart, liver and of the kidneys.

(ii) Sometimes the vomit, blood and pus or even a loose toothplate may get into the air passages during the stage of deep narcosis and afterwards cause aspiration pneumonia or bronchial block.

(iii) On account of vaso-dilatation and depression of the heat-regulating centre during the period of anæsthesia, there may be much loss of body heat, causing dangerous collapse or pulmonary complications. In such cases post-operative shock is also greater.

Many of these after-complications may be prevented by giving the patient one ounce of glucose in a pint of water 3 to 4 hours before the anæsthesia and afterwards more glucose also insulin in bad cases. Care should also be taken to keep the mouth empty, the body warm and always to watch the depth of narcosis.

Other precautions.—(i) Chloroform used, should be pure and stocked away from light and heat and as it undergoes chemical changes when mixed with air, it should not be kept in half-filled bottles.*

(ii) The condition of the heart and the lungs must be carefully examined before giving the anæsthetic. Valvular diseases and degeneration of the heart-muscles require special care, whereas considerable fatty changes more strongly forbid chloroform.

(iii) In diabetes mellitus, especially if the urine contains any acetone, chloroform is badly borne and unsuitable : it may in such cases induce coma.

SOME PRACTICAL HINTS.—No food is given within 3 to 4 hours before the anæsthesia and at the same time, long hours of fast is also undesirable. Before the anæsthetic is given, the mouth is made empty : the false or very loose teeth, if any, are removed. All clothing must be loose and the body, well-covered to prevent any excessive loss of heat during anæsthesia.

If a basal narcotic is not given, at first the anæsthetic is administered at a low concentration. This is less unpleasant, excites less struggle and does not produce any strong reflex effect on the circulation. At no period, a concentration of it in the air inhaled, 2% should be exceeded and 1% is usually sufficient.

If nevertheless, the respiration becomes shallow and feeble or if it ceases, the anæsthetic should be stopped, the mouth of the patient opened, the tongue pulled out and if necessary, CO₂ and O₂ with artificial respiration should at once be started.

* Carbonyl chloride, hydrochloric acid and chlorine are formed.

$$4\text{CHCl}_3 + 3\text{O}_2 = 4\text{COCl}_2 + 2\text{H}_2\text{O} + 2\text{Cl}_2$$

$$\text{COCl}_2 + \text{H}_2\text{O} = \text{CO}_2 + 2\text{HCl}$$

ETHER ANÆSTHETICUS (*Æther. Anæsth.*),

Anæsthetic Ether, (C₂H₅)₂O

Anæsthetic Ether is purified diethyl ether, to which a suitable stabiliser not more than 0·002% w/v added. Ether is prepared by distilling a mixture of ethyl alcohol and sulphuric acid and rectifying the distillate.

A colourless transparent, very mobile liquid with characteristic odour and sweet burning taste : very volatile and inflammable : its mixture with air, oxygen or nitrous oxide is explosive. Soluble at 15·5° in 8·5 of water : freely soluble in alcohol (90%), chloroform and in fixed and volatile oils. Should be stored in a dry container, closed and protected from light. Ether with light and air forms acetaldehyde and peroxide bodies which are highly irritant to the air passages.

Spiritus Ætheris (*Sp. Æther.*), See p. 54. DOSE, 15 to 60 minims or 1 to 4 ml.

ETHER SOLVENS (*Æther Solv.*), Solvent Ether, (C₂H₅)₂O.

Solvent Ether is diethyl ether and prepared in the same way as anæsthetic ether.

Solvent Ether is used in the preparation of *Collodium Flexile* and *Tinctura Lobeliae Etherea* (Not official).

Pharmacology [and Therapeutics]

Although as early as 1842, ether was used for surgical anæsthesia by Long in America, it was not as popular as chloroform for a long time but is now largely used.

The action of ether is very much similar to alcohol and chloroform except for the intensity.

APPLIED EXTERNALLY.—If allowed to evaporate from the skin surface, it does so quicker than either alcohol or chloroform and is a more powerful local refrigerant and anæsthetic. But if the evaporation is prevented, it is a more powerful rubefacient and vesicant.

Solvent ether is used in pharmacy for exhausting drugs like male fern and capsicum and as a solvent for substances like oils and resins : it is also used for cleaning the skin before surgical operations.

TAKEN INTERNALLY.—On the mouth and the stomach, the same action is repeated. Thus, taken orally, in dilute solution, it acts as a **vaso-dilator** and **reflex stimulant**. It gives a feeling of generalised warmth to the body and also acts as a **stomachic**, **carminative** and **cardiac accelerator**³¹⁷⁻³¹⁸. With a bigger dose, it induces, a certain amount of drunkenness resembling the same of alcohol but no true anæsthesia. It is however, absorbed

(317) R

Sp. Ammon. Aromat.

Sp. Chlorof.

Sp. Æther. aa. min. 15

Tinct. Cardam. Co. min. 30

Aq. Menth. Pip. ad. fl. oz. 1

A diffusible stimulant and res-
torative.

(318) R

Sp. Ether

Sp. Camph.

Sp. Menth. Pip. aa. min. 120

Misc.

20 drops to be taken every
2 hours for flatulence and intestinal
colic.

more rapidly from the colon-rectum and is sometimes given per rectum for **general anæsthesia**.

On the Heart and Lungs.—Apart from its action as a reflex accelerator through the mucous membrane of the stomach, it was thought to be a **direct stimulant** to both circulation and respiration [and was prescribed in acute fevers, like pneumonia and typhoid fever when the circulation was failing]. The pulse generally gains in fulness, thus giving an impression of being stronger, but it is doubtful if the heart muscles are really strengthened.

Increased fulness of the pulse is probably the effect of a slight vascular paralysis inducing sufficient vaso-dilatation to reduce the peripheral resistance thereby facilitating cardiac contractions. It reflexly **stimulates** the **respiration** also. [In acute collapse, ether is sometimes injected intramuscularly* for its reflex action on the circulation and the respiration].

NERVOUS SYSTEM.—Ether like chloroform is frequently used as an **anæsthetic** by inhalation. It is absorbed into the blood, taken up both by the corpuscles and the plasma and carried to the different parts of the body. It shows its specific action on the brain mainly on account of greater vascularity.

(1) The main *advantage* claimed for it, is (i) its **less depressant** action on the **heart** muscles and circulation generally. (a) From experiments with isolated hearts of mammals through which blood containing ether or chloroform was made to flow, it appeared that although both caused a certain amount of diminished force of contraction, in order to bring the heart to standstill, the concentration of ether required was at least 25 times more than that of chloroform. Further, chloroform concentration in the blood sufficient for anæsthesia may damage the heart muscles but not ether as required for the same purpose.

(b) Chloroform depresses the vasomotor centre and much more so the blood vessels themselves by direct action; so these are dilated, this dilatation being specially marked in the splanchnic area. The blood pressure falls, being partly due to vasodilatation and partly to cardiac depression. Ether, perfused through the blood vessels, dilates them in much the same way but to a less extent. But on account of partial asphyxia that it causes, this action is opposed by stimulation of the vasomotor centre.

During ether anæsthesia, the blood pressure slightly rises in the first and the second stages: in plane 3 of the third stage, it reaches the preanæsthetic level or goes slightly lower but does not reach the stage of grave circulatory failure.

(ii) **Respiratory centre** is also less depressed. Immediately following ether inhalation, especially if in high concentration,

* Ether. min. 10 to 15, intramuscularly, for sudden syncope.

the respiration may become feeble and shallow or it may stop : this may be the reflex effect caused by the irritating vapour of ether as happens with chloroform. It may also be due to inhalation of ether in high concentration, the cerebral circulation receiving the drug in an over dose. But on temporary suspension of administration, the respiration is soon re-established.

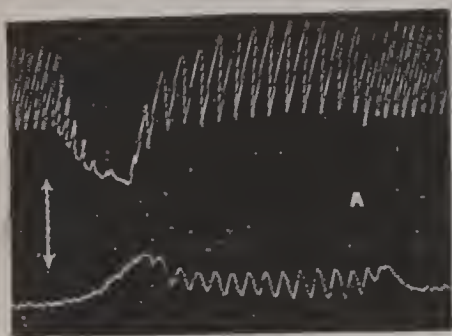
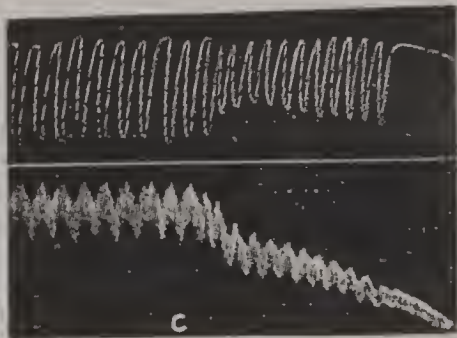


Fig. 24.—The upper tracing is of respiration and the lower of blood pressure. Ether inhalation is started at the arrow. The respiration after a drop, goes up : slow and deep. Blood pressure is not much affected.



(Cushny)
Fig. 25.—The upper tracing is of respiration and the lower of blood pressure. Chloroform in concentrated form is started at C. Blood pressure falls rapidly, respiration stops, ending fatally.

Chloroform is about 3 times more depressant to the respiratory centre. A strong vapour of it however, may cause reflex stopping of the respiration and in some cases direct depression also. As a concentrated vapour of chloroform may cause gross myocardial damage, the respiratory failure may be followed by the circulatory collapse ending fatally.

Death during ether anaesthesia on the operation table is very rare. In the few cases that have been described, the cause of death seemed to have been asphyxia, and primary paralysis of the heart, which is common in chloroform, has not been observed with certainty in ether narcosis. Ventricular fibrillation is unknown.

Relative toxicity of ether and chloroform on respiration is 1 to 3, central nervous system, 1 to 3 or $3\frac{1}{2}$ and on circulation, 1 to 25 or 30.

(iii) Ether is free from any injurious effect on the metabolism and does not produce many of the after-effects mentioned under chloroform. Chloroform anaesthesia especially if prolonged, causes liver damage shown by diminished elimination of bromsulphthalein dye given intravenously : dye is retained for a week or more. After ether anaesthesia, there may be slight delay in excretion but that is normal again on the next day.

(2) Ether has its disadvantages also. (i) It is a much weaker drug and requires to be given in a much more concentrated

form than chloroform. Chloroform in about 25 to 35 mg. per 100 c.c. of blood causes anæsthesia and 40 to 70 mg. per 100 c.c. respiratory failure. But ether 100 to 110 mg. per 100 c.c. of blood causes light anæsthesia : 130 to 140 mg. per 100 c.c. causes deep anæsthesia and 160 to 170 mg. per 100 c.c., respiratory failure. Comparing the vapour concentration per 100 volume of air it has been found that, while chloroform, in 1 to 1½% concentration is ample, ether requires 3 to 3·5% to cause anæsthesia (being 3 to 3½ times weaker in its effect). Even this higher concentration necessary for ether, leaves a safe margin for the heart and circulation and this is the great point in its favour. To obtain the concentration, a gauze face mask is used on which ether is dropped fairly freely. A special-fitting mask has also been used and this is more economical and ensures proper concentration. As this causes **lack of oxygen**, a prolonged ether administration is undesirable unless oxygen is also given at the same time. Ether may, however, be given in a less concentrated form, provided sufficient anæsthesia has already been induced either by Nitrous Oxide or Chloroform and Ether is used only to keep it up.

(ii) Ether, by itself, has the further disadvantage of having a **longer period of excitement** stage which if not shortened by a prompt narcotic in the beginning (pre-anæsthetic medication), is not liked either by the patient or by the surgeon.

In an alcoholic, ether sometimes fails to produce sufficient narcosis and in operations in the mouth, where the mask has to be taken out several times, a narcosis of sufficient depth may not be maintained.

(iii) Another difficulty is that ether vapour is highly inflammable and heavier than air ; so if the operation is performed with an open light or by thermocautery, it may **catch fire**.

(iv) Ether, especially when its vapour is concentrated, often causes both in men and animals, (a) pulmonary complications with a **profuse secretion of mucus** in the mouth and throat, which being aspirated in, may cause lung complications. By taking proper precautions to avoid this aspiration, as by lowering the head, wiping out the mouth and throat and using the drug in lowest possible concentration, these complications are often avoided. In other cases, a more serious complication as **massive collapse** of the lower lobes of the lungs may follow. Yet barring acute diseases of the lungs and pulmonary tuberculosis even in chronic bronchitis, with proper care, ether may be used.

(b) Although both chloroform and ether anæsthesia may cause albuminuria in some cases, chloroform is more harmful to the kidneys and may cause typical fatty degeneration. In **fatty heart** and in **nephritis**, chloroform should never be used alone, ether being more preferable.

(v) Further ether should not be used in acidosis and in increased intracranial pressure and also in acute pulmonary affections and pulmonary tuberculosis.

In spite of these disadvantages, on account of its less toxic action, ether is largely replacing chloroform.

When a prolonged anæsthesia is necessary, especially in a case like intestinal obstruction where the patient is already suffering from peritoneal shock, chloroform should better be not used. The anæsthesia may be started with a basal narcotic but afterwards maintained with ether.

AFTER EFFECTS OF ETHER ANÆSTHESIA

(i) *Vomiting*.—This is a frequent sequel and nausea may persist for 2 to 3 days with a distaste for food : with it may be associated headache, lassitude and sometimes a persistent taste of ether in the mouth. Ether is slowly eliminated from the system and so its smell hangs about for a long time and this is one of the reasons why the patient does not like ether anæsthesia.

[If vomiting persists, it should be considered to be partly due to acidosis and treated with isotonic glucose solution per rectum and insulin. Thirst is often much marked and is partly due to persistent vomiting. Bits of ice to suck and green cocoanut water to drink are helpful].

(ii) *Ether evaporates very rapidly* and this considerably cools down the vapour inhaled : a part of the respiratory troubles is ascribed to inhaling this extra-cool air. This may be avoided by putting the container in hot water at the time of administration so that a warm vapour is inhaled.

(iii) *Convulsive movements* may sometimes occur late in anæsthesia. These commence from the face and spread to other parts of the body and may end fatally. The exact mechanism is yet undetermined.

If very violent and persistent, chloroform inhalation and intravenous injection of sodium pentothal may control the movements.

RECTAL ETHER ANÆSTHESIA.—The rectum is first washed with normal saline and ether 3 parts and olive oil 1 part are slowly introduced. Anæsthesia follows in ten minutes. 1 oz. is given for every 20 lb of body weight, 8 oz. being the maximum dose. Rectum is washed out again after the operation. But the anæsthesia is often incomplete and there may be local irritation of the bowels.

Treatment of the Untoward Symptoms of General Anæsthesia

(i) **CYANOSIS.**—This may be due to excessive bronchial secretion, the falling back of the tongue, the jaw, or the paralysed epiglottis or too much turning of the head on one side : these should at once be looked into.

In a case of respiratory embarrassment, the anæsthesia should be at once stopped and a respiratory stimulant like caffeine or atropine

immediately injected ; if necessary, artificial respiration should be started and also the administration of oxygen with carbon dioxide.

(ii) FOR FAILING CIRCULATION.—The anæsthesia is stopped. Analeptics as coramine or leptazol is given subcutaneously or intravenously and blood plasma intravenously : the foot-end of the bed is raised and fresh air or oxygen freely given.

(iii) VOMITING DURING ANÆSTHESIA.—The vomiting reflex is entirely lost during the stage of deep anæsthesia. So vomiting during an operation indicates that the patient is not sufficiently under and requires a deeper anæsthesia. Further, when the patient is coming out of anæsthesia, he often vomits. At that time, the muscles of expulsion are more or less paralysed and if sufficient care is not taken, a part of the vomit that remains in the mouth may enter the respiratory tract and set up aspiration pneumonia. So in such a condition, the head should be slightly lowered and turned on one side and anything that comes into the mouth should at once be taken out of it with a towel or a sponge.

Non-official Preparations

SPIRITUS ÆTHEERIS COMPOSITA.—*Hoffmann's Anodyne.* Sulphuric acid 36 fl. oz. and alcohol (90%), 40 fl. oz. are mixed and distilled after 24 hours and a little sodium bicarbonate is added to neutralise the acid. A complex compound called oil of wine is formed. To this is added ether 5½ fl. oz. and alcohol (90%), 38 fl. oz.

Dose, 60 to 90 minims. A stimulant and carminative.

METHYLATED ETHER.—Made from commercial methylated spirit, may be used for external use and is not suitable for general anæsthesia.

ÆTHER VINYLICUS (*Æth. Vinyl.*), $(CH_2:CH)_2O$

Vinyl or divinyl ether to which have been added a stabiliser as dehydrated alcohol 4% by volume and not more than 0.01% of phenyl- α -naphthylamine, is prepared by the action of pot. hydroxide on beta-beta'-dichlorodiethylether and subsequent purification.

A clear colourless, inflammable liquid with a purplish fluorescence and characteristic smell. Soluble in 100 parts of water and freely in alcohol 90%, solvent ether and in chloroform. Should be kept in a wellclosed container of not more than 200 ml. capacity.

Pharmacology [and Therapeutics]

Divinyl ether is a rapidly acting volatile general anæsthetic. It may be given by open, semi-open or closed method with the usual gas machines.

Anæsthesia is induced rapidly in 1 to 1½ minutes : the patient goes under without any period of excitement, struggle or coughing. When further administration is stopped, recovery takes place in less than five minutes without any after-effect or nausea : unlike ether, there is not much irritation to the respiratory tract.

A blood concentration of 18 mg.% causes third stage of anæsthesia as compared with 130 mg.% of ethyl ether and thus it is more powerful. Muscular relaxation is nearly the same as of ether.

The signs of anæsthesia are not too obvious : main reliance is to be put on the character of respiration : its rate is slightly

increased and it is shallower. Fatal cases are from respiratory failure. Cardiovascular system is not directly affected. Judiciously used, especially by an experienced anaesthetist, short operations may be conveniently performed without complications: these are on the nose, mouth (especially dental), eye and the throat also short obstetric operations. Further, it is suitable for inducing general anaesthesia to be kept up by ether. In no case it should be used for more than half hour as it may damage the liver.

Open method of administration by dropping into the mask is suitable. Care should be taken against *fire and explosion*. It may cause salivation and a preliminary injection of atropine is helpful.

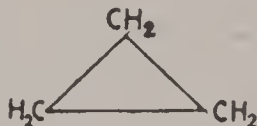
It is toxic to the liver causing degenerative changes like chloroform. So it is contra-indicated in hepatic and also in renal and cardiovascular diseases.

The bottle once opened should not be kept for more than 24 hours as it deteriorates on exposure to air.

CYCLOPROPANUM, (*Cycloprop.*), Cyclopropane, C_3H_6

Cyclopropane gas may be prepared by the action of zinc on 1:3-dibromopropane containing not less than 99% v/v of C_3H_6 : supplied compressed in metal cylinders. Waters and Schmidt (1934) first used it clinically as a general anaesthetic.

An inflammable, colourless gas with characteristic sweetish odour: is explosive in mixture with air in concentration of from 20 to 75%, and oxygen, even in 3.8%. One volume dissolves in about 2.7 volumes of water at 15°: very soluble in alcohol (90%), solvent ether and in chloroform.



Pharmacology [and Therapeutics]

Cyclopropane is a powerful volatile general anaesthetic causing analgesia without unconsciousness in continuous inhalation at 5%: plane 1 anaesthesia at 7.5%: plane 2, at 13% and plane 3, at 23.3% with premedication with morphine: without morphine, 26% produces plane 2. Toxic concentration at plane 4 is 43%: so there is thus a good safe margin. The induction is pleasant but takes a little longer time than nitrous oxide, taking 1 to 3 minutes: muscular relaxation is moderate but less than that of ether. It is nonirritant and does not cause much vomiting or respiratory complications. A higher concentration as 20% of oxygen can be given with it and cyanosis is not marked even with deep anaesthesia. Variations in amplitude of *respiration* also are not as obvious. These made it difficult to estimate the degree of narcosis. *Pupil* is often dilated even if morphine is previously given as premedication. But as the margin of safety is high with an experienced anaesthetist, no serious consequences follow.

Cardio-vascular signs of overaction are more obvious. These are **cardiac irregularities** of ventricular type either bradycardia (rate of 50 per minute is an indication to stop further administration), tachycardia or extrasystoles. Blood pressure is not lowered. Further inhalation being stopped, recovery is quick without obvious after effects.

Recovery takes place within a few minutes of stopping administration. Nausea, vomiting, pneumonia and pulmonary collapse are less frequent than of ether. It is not toxic to the liver.

Advantages.—It is a safe volatile anæsthetic, 15% of cyclopropane being usually needed: oxygen may be administered with it in high concentration and it has no marked toxicity on the circulation, respiration and the liver. It is specially useful in thoracic surgery (quiet respiration) and in pregnancy, (especially in obstetrical operations), circulatory deficiencies, pulmonary diseases and in exophthalmic goitre (high oxygen level maintained). If muscular relaxation is not sufficient, a little ether may be supplemented.

Disadvantages.—This is mainly, a liability to *explosion* if used near an open fire. The range is 3 to 8.5% in air and 2.5 to 50% in oxygen. A tendency to *capillary oozing* observed by some has not been confirmed.

It is administered with a special apparatus along with oxygen having a CO₂ absorption arrangement. In the beginning, cyclopropane only is administered for 3 minutes and then this is shut off and oxygen administered: more cyclopropane may be necessary if anæsthesia is insufficient. Premedication with morphine-atropine, pethidine and amytal prevents cardiac irregularities.

NITROGENII MONOXIDUM (*Nitrogen. Monox.*), Nitrous Oxide, N₂O

Nitrous oxide is prepared by heating ammonium nitrate and is supplied in metal cylinders. It contains not less than 95% v/v of N₂O. This is a colourless gas heavier than air with a characteristic odour and faintly sweetish taste.

Pharmacology [and Therapeutics]

Although as early as 1798, Davy advised the use of Nitrous Oxide as a general anæsthetic, Wells used it clinically in 1846, it has become official in 1932 only. It is quite suitable for **short anæsthesia**.

To the tissues, nitrous oxide behaves as an indifferent gas because its oxygen is not separated from it at body temperature. But it has a special selective action on the *central nervous system*. On inhaling the undiluted gas, the action begins instantly. There is buzzing and ringing in the ears,

incoherent talk, uncontrolled movements and then consciousness is clouded and **analgesia** commences, associated with slight cyanosis. All these happen in the course of one minute. If the inhalation is now stopped, the anæsthesia lasts for only 20 to 30 seconds and the patient immediately wakes up feeling perfectly well.

Nitrous oxide is more easily dissolved in blood (lipids of the corpuscles taking it) than in water : at the beginning of anæsthesia, its *concentration in blood* is 40 mg.% : at complete anæsthesia, 50 mg.% and when the respiration fails, 60 mg.%. *Respiratory failure* is partly from asphyxia and partly from central depression. *Circulation* is not much affected. A slight rise in blood pressure and slowness of pulse is seen due to asphyxia. As the inhibitory centre is slightly depressed, the slowing is less than that of ordinary asphyxia.

ADVANTAGES.—The gas is administered from a cylinder where it is kept under compression. The circulation and the respiration are not as much depressed as by chloroform or ether. There is no post-operative complication. Return to consciousness is almost immediate.

For a short operation like the extraction of tooth, it is frequently used pure, without oxygen or only 5% of oxygen is added. Indication to stop further administration is marked cyanosis with noisy respiration. But for a more prolonged anæsthesia, oxygen is essential : 10 to 15% of it with the gas is needed, (*gas-oxygen anæsthesia*), and it requires skill to keep the patient in a state of sufficient narcosis without much asphyxia. A special mask has been devised by which the expired air goes out or CO_2 is absorbed and the patient breathes in N_2O and O_2 . For bigger operations, the combination of a basal narcosis with nitrous oxide-oxygen-ether is the safest method.

DISADVANTAGES.—The *muscular relaxation* is imperfect, the patient being in plane one anæsthesia. It is not, however, satisfactory for the alcoholics and also for fatty and robust athletic persons. It is *contra-indicated* in a child under 5 years, because of the ease with which asphyxia can be induced in them. As the blood pressure is raised, it is unsuitable for elderly people, in brain surgery and in persons with weak and fibroid heart muscles. It is explosive if mixed with ether and ethylene.

ÆTHYLENUM (*Æthylen.*), Ethylene, $\text{CH}_2 : \text{CH}_2$

Ethylene is obtained from the products of decomposition of petroleum. It should contain not less than 98% by volume of C_2H_4 . It is a colourless, inflammable gas with slightly sweet odour and taste, supplied compressed in steel cylinders. Surgical operation with ethylene was first performed in 1923.

Pharmacology [and Therapeutics]

Ethylene inhaled, causes **general anæsthesia** quickly without much irritation of the respiratory passages. Thus in 1 to 4 minutes, complete anæsthesia is obtained and on stopping further administration, the recovery is also as prompt, this resembling nitrous oxide and free from unpleasant side effects.

Administered with 10% of oxygen, it causes more profound anæsthesia with greater muscular relaxation than that of nitrous oxide although slightly less than of ether without causing respiratory irritation or cyanosis.

The plane 2 degree of anæsthesia is quickly reached and the patient is ready for a short operation. In some cases, a little ether may be necessary especially if the operation is prolonged and greater muscular relaxation is necessary. In such cases ethylene in 80% concentration is good enough.

The amplitude of contraction of the muscles of the stomach and the intestine may be increased during light anæsthesia but these become normal when full surgical anæsthesia is reached.

For obstetric analgesia, 25 to 50% of ethylene with air is sufficient till the head presents at the vulva: uterine contraction is not affected. The final operation may be performed with a little higher concentration of it.

Respiration is slow and regular and *pulse* is slightly quickened in the beginning and afterwards reaches normal and *blood pressure* is unaltered or only moderately lowered. *Pupil* is slightly contracted. In some cases *capillary oozing* may happen in the operation. *Renal and hepatic functions* are unaffected. *Blood alkalinity* may be slightly lowered.

It does not cause any sweating or fall in the temperature and has very few untoward after-effects.

As an after-effect, some nausea and vomiting may be present in the first 3 or 4 hours in about one-third of the cases but not as much as with ether. This has practically no effect on the circulation or on the kidneys.

Although recently introduced, it is gaining popularity on account of its efficiency and safety. It forms an *explosive mixture* with air and so should not be used in the presence of an open light: but a much higher proportion of oxygen is necessary for this than 10%, what is required for its use with an anæsthetic. Further, the gas is readily diffusible and an explosive concentration of it is lost beyond two feet from the mask.

ÆTHYLIS CHLORIDUM (*Æthyl. Chlor.*), C_2H_5Cl

Ethyl chloride is obtained by the action of hydrochloric acid on ethyl alcohol or industrial methylated spirit. It is gaseous at ordinary temperature and pressure.

It is condensed into a colourless fluid and put up in a glass tube with a fine point. When the stopper is opened, it immediately volatilises, the

boiling point being 12.5°C , and comes out in a fine jet. Has a feeble ethereal odour and burning taste. It is feebly soluble in water but freely so in alcohol (90%) and in solvent ether. It was discovered by Florens in 1847.

Pharmacology [and Therapeutics]

LOCAL ACTION.—Applied in the form of a fine spray from a distance of about one foot, on striking the warm skin, it vaporises with such rapidity that it **freezes the tissues**. This causes **local anæsthesia** of a moment's duration during which a small cut like the opening of an abscess or puncturing the skin for drawing out the pleural or peritoneal fluid can be done without much pain. The only drawback is that the tissue is hardened in the process which does not cut readily and may sometimes be so devascularised that it may slough out. Ethyl chloride is *explosive* and *inflammable*. It should be kept away from fire.

SYSTEMIC ACTION.—To produce **general anæsthesia**, ethyl chloride is sometimes vaporised in an inhaler and administered. The patient is anæsthetised in 1 to 2 minutes without causing any irritation to the air passages but the muscular relaxation is incomplete. There is no unpleasant or unfavourable symptom. The pulse is slowed and the respiration is made deeper. When the anæsthetic is stopped, the recovery is almost immediate and therefore although it is efficient for a **very short work** as tooth extraction or tonsillectomy, it is unsuitable for maintaining anæsthesia for any length of time. Thus 20 mg.% causes light anæsthesia : 30 to 150 mg.% deep anæsthesia and 40 to 180 mg.% respiratory failure : so it is unsafe for deep anæsthesia.

It is **less depressant** to the circulation than chloroform but ventricular fibrillation and sudden heart stoppage may occur. Like ether it causes **irritation of the respiratory passages**.

It is not usually used for general anæsthesia. As a local anæsthetic also, it is inferior to procaine but the simplicity of application is the advantage.

TRICHLOROÆTHYLENUM (*Trichloroæthylen.*), Trichloroethylene, CHCl.CCl_2

Trichloroethylene is prepared by chlorination of acetylene to give tetrachloroethane followed by treatment with lime and purification by distillation : thymol 0.01% may be added as preservative.

A colourless, transparent, mobile liquid with odour resembling that of chloroform : taste is sweet and burning. Bright light in the presence of air causes decomposition.

Nearly insoluble in water, miscible with dehydrated alcohol; solvent ether, chloroform and with fixed and volatile oils.

Pharmacology [and Therapeutics]

Trichloroethylene was used in industry as a solvent mainly in dry cleaning also for degreasing of metals and for oil and fat extraction. It was found that the workers got bilateral loss of sensation of the area of the distribution of the fifth cranial nerve (Plessner, 1915).

Therapeutically, this came to be used for the treatment of severe paroxysms of **trigeminal neuralgia**. Available in 1 c.c. glass tubes, one is broken and put at the bottom of a tumbler and inhaled : 3 or 4 tubes may be inhaled in this way. About 50% of patients get relief.

It is also used for the relief of pain of glossopharyngeal neuralgia, angina pectoris and migraine. The action is central, depression causing analgesia.

It has a pleasant sweetish odour and can cause general anæsthesia also (Jackson, 1934) but is not used as such.

Although fairly safe, it should not be *freely* used by the patient himself without control and supervision of the physician.

SUMMARY.—(i) For major surgical operations *chloroform* is less preferred than *ether* on account its greater toxicity on the medullary centres, heart muscles and on the liver. Ether although safer has a prolonged induction stage, causes irritation of the respiratory tract and pulmonary complications, frequently vomiting and rarely convulsions. So basal anæsthetics are often used first to cause partial anæsthesia which is kept up by ether or nitrous oxide, oxygen and ether combinations used. (ii) A **short anæsthesia** of a few minutes' duration may be induced by *nitrous oxide*, *vinyl ether*, *cyclopropane*, *ethylene* and *ethyl chloride*. Most of these require oxygen simultaneously especially if anæsthesia is to last for more than a few minutes and a little of ether also if the muscular relaxation is not sufficient : all except nitrous oxide are explosive with oxygen in the presence of fire. *Trichloroethylene* may be used as analgesic by inhalation in neuralgias. *Ethyl chloride* is analgesic by local application as a spray.

Non-official Preparations

ACETYLENE in 70% concentration is a fairly good general anæsthetic but its ready explosiveness is a disadvantage.

CYPRETHYLENE is a powerful anæsthetic and has to be given with oxygen : muscular relaxation is good.

THE CHOICE OF AN ANÆSTHETIC

The *Volatile* anæsthetics as chloroform, ether, divinyl ether, cyclopropane, nitrous oxide, ethylene and ethyl chloride are used by inhalation to be absorbed by the respiratory tract and the operator can regulate the depth of narcosis. But others are *non-volatile* such as paraldehyde, bromethol or avertin, barbiturates especially hexobarbitone soluble (sodium evipan), sodium amytal, pentobarbital sodium (nembutal) and thiopentonium soluble (pentothal sodium). The others are pernocton and morphine-scopolamine. There are given either per rectum or by intravenous or subcutaneous injection and the intensity of their action is difficult to regulate. So this group is more

suitable as basal narcotic to induce partial anæsthesia only, the rest being done either by ether or by nitrous oxide-oxygen. For general use, chloroform is convenient but it is more toxic and is not suitable in certain cases, especially in a patient in shock, with circulatory depression and in toxic goitre. In fact, in all major operations, it is often avoided.

Basal Narcotics

The main **advantages** of these are : (i) anæsthesia is induced without a state of anxiety or discomfort : (ii) the quantity of a volatile anæsthetic used is lessened : (iii) a period of post-operative rest and freedom from pain is obtained, also (iv) post-operative complications especially from bronchial and gastric irritations are lessened. The main **disadvantages** are (a) inability to precisely control the degree of narcosis and its duration : the latter if great, may cause hypostatic pneumonia : (b) most of these are unsuitable if the liver is diseased. Liver is the important detoxicating agent.

ALCOHOL TRIBROMOETHYLICM (*Alcoh. Tribromoethyl.*), Tribromoethanol, $\text{CBr}_3\text{CH}_2\text{OH}$.

Tribromoethyl alcohol, *Avertin* is prepared by reduction of tribromoacetaldehyde containing not less than 99% of tribromoethanol, $\text{C}_2\text{H}_3\text{OBr}_3$.

A white crystalline powder, unstable in air with slightly aromatic odour and taste. Soluble in about 35 parts of water at 25° ; the solution is unstable. Readily soluble in amylene hydrate and light petroleum. It should be stocked in dark bottles as exposure to light hydrolyses it to hydrobromic acid.

AMYLENI HYDRAS (*Amylen. Hydr.*), Amylene Hydrate $(\text{CH}_3)_2(\text{C}_2\text{H}_5)\text{C.OH}$.

This also called *tertiary amyl alcohol*, is dimethylethyl carbinol $\text{C}_5\text{H}_{12}\text{O}$, prepared by hydration of amylene.

A clear, colourless, volatile liquid with pungent burning taste and camphoraceous odour : soluble in 8 parts of water : miscible with alcohol (90%), solvent ether, chloroform and with glycerin.

Dose, 30 to 60 minims or 2 to 4 ml.

BROMETHOL (*Bromethol*)

This is a solution of tribromoethyl alcohol, *Avertin fluid*, containing tribromoethyl alcohol 66.7 g. and amylene hydrate 33.3 g.

Preparation of a solution for rectal injection.—For use by rectal injection, bromethol is diluted immediately before administration with 39 times of distilled water at 40° , being dissolved by vigorous agitation.

To 5 ml. of this solution is added 0.2 ml. of congo red solution : the colour must remain red or orange red.

Dose by rectal injection as a *basal anæsthetic*, $\frac{1}{2}$ to $\frac{2}{3}$ minim per pound of body weight or 0.075 to 0.1 ml. per kg. of body weight.

Avertin is a new basal anæsthetic. About 0.1 ml. per kg body weight or slightly less of avertin fluid (bromethol) given in 30% or more diluted watery solution, moderate

warmed, by enema 30 minutes before an operation. It is rapidly absorbed 50% in 10 and 95% in 25 minutes, and causes deep unconsciousness by selective depression of the central nervous system: but a dose necessary for full surgical anaesthesia is not considered safe and a small quantity of ether or nitrous oxide-oxygen by inhalation is administered for complete muscular relaxation. It is thus used as a basal narcotic only. The anaesthesia persists for one to three hours and a post-operative sedative is not required.

It is largely absorbed into the general circulation, detoxicated by the liver combining with glucuronic acid to form urobromic acid and is excreted in the urine: 75% in 48 hours and complete elimination requires 7 days.

It is *suitable* for operation on the head, pulmonary diseases and in exophthalmic goitre, but *unsuitable*, (a) if any inflammatory condition is present in the colon or (b) there is advanced liver, heart or kidney disease: (c) also unsuitable in old age, obesity, diarrhoea, acidosis and in a condition of shock.

ADVANTAGES.—(i) The patient is anaesthetised pleasantly usually without a stage of excitement, irritation of the respiratory tract or vomiting, (ii) It causes slight decrease of intracranial pressure and is thus suitable in brain surgery.

DISADVANTAGES of this as of other non-volatile anaesthetics are (i) that the intensity and duration of narcosis is not quite under control and careful nursing is necessary during the whole period of anaesthesia.

(ii) It is a more *powerful depressant* to the respiratory centre than even chloroform and with a bigger dose, vasomotor centre is also depressed. Blood pressure tends to fall and the pulse rate is increased.

(iii) General metabolic rate falls and glycogen in the liver is largely depleted. Blood sugar level rises. In the urine albumin appears in a fair number of cases. Given in bigger doses, degenerative changes have been found in the liver, kidneys and in the colon.

Maximum safe dose for a woman is 6 ml. and for a man, 9 ml. and nothing more than basal narcosis should be aimed at.

In smaller doses, this has been used in the second stage of labour for making labour pain less felt ("twilight sleep") and also in various convulsive states as tetanus, epilepsy and eclampsia.

AMYLENE HYDRATE is a *hypnotic*, 2 to 3 times stronger than paraldehyde but weaker than chloral hydrate. Its depressant effect on the circulation is also intermediate between these two. There may be a preliminary stage of cerebral excitement and the hypnotic action is less certain than of chloral and is consequently less frequently used. Its main use is in the preparation of avertin fluid.

Other basal narcotics as paraldehyde, barbiturates morphine, pethidine and scopolamine have been taken up in other places.

III. HYPNOTICS

Sleep is the natural phenomena usually coming at certain hours of the night and is the consequence of day's exertion and fatigue. In certain pathological conditions often a systemic infection, intoxication or a gross lesion, also for pain, worries, excitement and disturbed surroundings, the natural sleep is absent and drugs have to be used.

HYPNOTICS (G. *hypnos*, sleep) are drugs that cause sleep by directly depressing the activities of the cerebral cells. In other words, hypnotic drugs are mildly narcotics. Their action somewhat resembles that of general anæsthetics but is slower in onset, without any stage of excitement, less powerful, more lasting, continuing for several hours and is not intended to go up to the stage of deep insensibility.

Further, the *intensity of the action* of these is variable, depending on the dose given. With a gradually increasing dose, the following effects are produced in succession.—

(i) *Stage of Diminished Psychic Functions* causing sleep from which the patient can be awakened. But if any painful condition is present, sleep does not follow. For therapeutic purpose, only this type of action is wanted.

(ii) *Stage of Diminished Reflex Function*.—The reflexes are sluggish and co-ordination is impaired. This effect sometimes happens even without hypnosis.

(iii) *Stage of Analgesia*.—The patient is semicomatose and has very little sense of pain. The corneal reflex is feeble.

(iv) *Stage of Surgical Anaesthesia*.—The patient is completely unconscious and the corneal reflex is lost.

(v) *Stage of Medullary Paralysis* ending fatally.

Ideal hypnotic.—To be useful in practical therapeutics, the drug (i) *should* only moderately depress the cerebral centres without any preliminary stage of excitement: should be pleasant to take, be water-soluble and readily absorbed from oral administration to have the action within a short time and excreted or partly destroyed in the system fairly quickly to have the effect for a limited period only. (ii) It *should not* have much after-effects on the next day, not depress the medullary centres nor have any disadvantageous side action and not form a drug habit.

In a person suffering from persistent insomnia, the risk of formation of drug habit is great. The general rule, therefore, is not to repeat the same drug too often by changing the prescription frequently and also to try and see if the patient can do without any hypnotic at all.

A **psychic factor** is also often associated with insomnia. If sleep is induced by a powerful hypnotic flavoured with a milder one but having a strong smell (like paraldehyde), it may soon be possible to obtain sleep with paraldehyde alone. If an injection of morphine was being given, the same of distilled water may subsequently suffice.

There are three grades or degrees of cerebral depression which may be necessary for sleep and the choice of a hypnotic varies accordingly.

(1) **BRIEF MILD DEPRESSION.**—When a person is otherwise healthy but cannot get sleep on account of fatigue, anxiety or restlessness, a dose of *alcohol* as brandy or a *bromide* (sodium, potassium or ammonium) may be sufficient to cause a mild degree of cerebral depression and sleep.

Here the depressant action is mainly on the *cerebral cortex*.

(2) **PROLONGED MILD DEPRESSION.**—This is necessary both to induce sleep and to maintain it for a length of time, when the normal tendency to sleep seems to be absent, as in fevers, neurasthenia and in various kinds of nervous disorder.

The drugs of this group are called **Aliphatic Hypnotics**. These except paraldehyde, act probably on the *thalamic* and the *subthalamie regions*. These may be divided into.—

(a) *Chloral Hydrate group* including Chloral Hydrate, Butyl-chloralhydrate, Chloralamide, Glucochloral and Chlorbutol.

(b) *Ethylated compounds*, as Sulphonal, Methylsulphonal, Barbitone group, Avertin, Amylene hydrate and Urethane.

(c) *Aldehydes*, as Paraldehyde : but this acts on the *cerebral cortex*.

(3) **PROLONGED DEPRESSION WITH ANALGESIA.**—This is specially indicated to induce and maintain sleep where pain or any other powerful factor keeps the patient awake. The best example of this type is *morphine* also pethidine, codeine, diamorphine, papaverine and eukodal.

Analgesic antipyretics as phenazone, phenacetin, amidopyrin or aspirin are also slightly hypnotic.

Two other drugs have hypnotic properties : these are *scopolamine* and *cannabis indica*. The former is a powerful sedative and is useful in maniacal conditions but the latter is uncertain in its action and is seldom prescribed for this purpose.

BROMIDES

1. **POTASSII BROMIDUM** (*Pot. Brom.*), Potassium Bromide, KBr.

Colourless, transparent or opaque cubical crystals or white granular powder, with a salty taste, soluble in about 2 of water and 200 parts of alcohol (90%) : obtained by the action of ferrous bromide on potassium carbonate. It contains not less than 98.5% of KBr dried at 110°.

Dose, 5 to 20 grains or 0.3 to 1.2 grammes.

Tabellæ Potassii Bromidi (*Tab. Pot. Brom.*), See p. 58. If not otherwise stated, each tablet contains 5 grains. Dose, Same as of Pot. Brom.

2. **SODII BROMIDUM** (*Sod. Brom.*), Sodium Bromide, NaBr.

Prepared by the action of ferrous bromide on sodium carbonate. Slightly deliquescent, granular, white powder or colourless transparent or opaque cubic crystals, inodorous and with slightly bitter saline taste :

soluble in 1.5 of water and in 16 parts of alcohol (90%). It contains not less than 98.5% of NaBr, the substance being dried at 113°.

DOSE, 5 to 20 grains or 0.3 to 1.2 grammes.

INCOMPATIBLES.—All acids and acid salts, metallic salts and strychnine are incompatible with bromides. Acids liberate bromine.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, on the intact skin, the bromides have no action.

TAKEN INTERNALLY, any of these salts shows three kinds of action :

- (i) *Salt action* on the stomach and the intestine.
- (ii) *Specific action* on the nervous system, at first on the psychic and motor centres of the brain and then on the medulla and the spinal cord.
- (iii) *Irritant action* in the process of excretion.

A bromide has a slightly **bitter salty taste**, increasing the flow of saliva. Taken in big doses and in concentrated form, it abstracts fluid from the mucous membranes of the stomach and intestine and like other salts, may cause **vomiting** and more rarely **purging** from local salt action. Therefore in therapeutic administration, a bromide should be given well diluted with water or after a meal. These effects are less marked with sodium bromide which is sometimes preferred.

A bromide is quickly absorbed from the intestine in the form of its sodium salt. It attains the maximum concentration in the blood and passes therefrom into all tissue fluids and secretions. It exerts its action from the extracellular fluid and does not specially concentrate on or absorbed by the cells. Having no special action, except on the brain, the tissues do not make any differentiation between bromine-ion and normally present chlorine-ion and so when a bromide is given by the mouth, it replaces the normal chloride and tends to accumulate in the body fluid and transudates, without altering the normal salt concentration. The activities of the muscles, the heart and even of the peripheral nerves are not appreciably altered if perfused with a bromide solution.

NERVOUS SYSTEM.—A bromide shows its direct specific action on the cells of the central nervous system and **depresses the functions of the brain** (the psychic and the motor areas and with big doses, slightly the sensory also), **medulla** and the **spinal cord** (the reflex functions). The different areas are affected almost simultaneously and so, unlike alcohol, there is no stage of uncontrolled activity of the lower centres. The reflex activities are lessened due probably to depression of the path of communication between the motor and sensory cells of the spinal cord and between the sensory path and the cerebral cortex. But the connection between the cerebral centres and motor cells of the spinal cord remains intact. With bigger

doses as 30 grains 3 times daily, the acuteness of perception is also diminished.

(i) The action starts with a feeling of lassitude and disinclination for all kinds of work, mental or physical. There is some confusion of ideas and blunting of memory. This stage of apathy soon develops into drowsiness and sleep. A bromide is therefore a valuable **hypnotic** (first used by Behrend in 1864), and is specially useful when *no pain is present*. Although not as powerful as chloral hydrate or a barbiturate, it is specially indicated when either mental worry or excitement is the cause of wakefulness³¹⁹. But sometimes the sleep that follows is not refreshing and as the elimination is slow, a dull feeling hangs over till the next day. A single dose at bed time may fail, sufficient concentration of the drug in the extracellular fluid not being reached.

(ii) On account of the depressant action on the excitability of the *motor cells* of the brain, it is specially valuable in all kinds of **convulsive attacks** [as in epilepsy^{320,321}]. Bromine-ion is to replace the chlorine-ion in the extracellular fluid in the brain; in order to bring the patient quickly under the influence of bromide and to maintain that effect, sodium chloride in the food is restricted and blood concentration of 72 to 100 mg.% or a little higher is obtained and maintained. But if continued too long, the bromide causes apathy, languor and mental dullness with deterioration of the mental faculties and degeneration of some of the cortical cells. In such cases one method of favouring elimination of the bromide is to increase the chloride in the dietary. For prolonged administration, the bromide has been largely replaced by barbiturates and other synthetic anticonvulsants.

(iii) A bromide is sometimes useful in the **nervous excitement** of hyperthyroidism, hysteria, cardiac arrhythmia and in anxiety neurosis.

(iv) In the same way, by its action on the medulla and spinal cord, the reflex functions are markedly diminished [and a bromide is given in many kinds of **spasmodic conditions** as in hysteria³²², whooping cough, dysmenorrhœa, chorea, laryngismus stridulus (spasmodic contraction of the larynx) and in tetanus.

- (319) R
 Pot. Brom. gr. 15
 Chloral. Hydr. gr. 10
 Syr. Aurant. min. 60
 Aq. Chlorof. ad. fl. oz. 1
 Hypnotic and antispasmodic.
- (320) R
 Pot. Brom.
 Sod. Brom.
 Ammon. Brom. aa. gr. 5
 Sp. Chlorof. min. 20
 Aq. ad. fl. oz. 1

A hypnotic also a sedative for epilepsy.

(321) R
 Pot. Brom. oz. 1
 Ammon. Brom. gr. 180
 Pot. Iod. gr. 120
 Ammon. Carb. gr. 60
 Tinet. Calumb. fl. oz. 1
 Aq. ad. fl. oz. 6 (Martindale)
 For epilepsy, 60 to 120 min. per dose well diluted.

manifestation of *chronic poisoning*. These are nervous, cutaneous, gastrointestinal and glandular. *Nervous depression* is more important and shown by the lowering of mental capacity, disinclination for mental and physical work, lethargy and rarely coma. Mental changes may be of the nature of disorientation, delirium, delusion, hallucination and even maniacal state; lessening of *reflexes* superficial and deep, sluggish pupillary reflexes, *tremors* and apraxia may sometimes appear: *tachycardia* and slight rise of *temperature*, may be seen. These are more marked in elderly persons with arteriosclerosis. The *skin eruptions* are pustular on the face and nodular on the extremities. Occasionally the buccal and the bronchial *mucous membranes* are inflamed, resulting in digestive disturbances (hydrobromic acid appears in the gastric juice) and increased bronchial and lachrymal *secretions*. This toxic symptoms are called "**Bromism**". Further administration should be immediately stopped and large doses of sodium chloride given.

Acute poisoning is very rare: may be intentional or accidental swallowing of a large quantity. There is deep sleep with stupor for several hours and apathy and mental confusion may last for several days.

Bromides are now less commonly used than before as more powerful and less toxic drugs are available.

SUMMARY.—A bromide is *quickly absorbed* from oral administration and accumulates in the extracellular fluid by replacing chlorides. It is inert to all tissues except the **central nervous system** to which it is an universal depressant: it is a *hypnotic*, *anticonvulsant*, *psychic sedative*, *antispasmodic* and inhibitor of *reflex functions*. It is slowly excreted and may cause *cumulative poisoning* (bromism).

Non-official Preparations

AMMONIUM BROMIDE.—Colourless cubic crystals with a pungent saline taste, soluble 1 in 1.5 of water.

Dose, 5 to 30 grains.

BROMIDIA, 60 minims contains chloral hydrate and potassium bromide, each 15 grs. and extracts of cannabis indica and hyoscyamus, each 1/5 gr. Dose, 30 to 60 minims.

BROMOFORM, (tribromomethane) a colourless liquid: used for mental excitement and in whooping cough.

Dose, ½ to 2 min. used as elixir or syrup.

BROMURAL, Bromoisovalerianylurea.

Dose, 5 to 10 grains, is a good rapidly acting hypnotic, the action lasting for 3 to 5 hours and is a nerve sedative.

CHLOROBROM, one fl. oz. contains 30 grs. of each of chloralamide and potassium bromide flavoured with liquorice.

Dose, ½ to 1 fl. oz. as hypnotic.

CALCIUM BROMIDE (10 to 20 grs.). **BROMINAL** (10 to 60 grs.), **BROMETONE** (5 grs.) are used for bromide action.

PEACOCK'S BROMIDE contains in 60 min, 15 grains of bromides, sodium, potassium, calcium, ammonium and lithium: frequently used for bromide action.

ELIXIR BROMOVALERIANATE, each fl. dr. contains bromide 10 gr. and chloral hydrate 5 gr. with valerian, cannabis and hyoscyamus. See p. 133.

SEDOBROL, Roche, is a special form of sodium bromide obtained as cubes each equalling 1.1 g. Liquid 3 c.c. equals one cube: palatable, may be taken with food.

SALIX NIGRA.—The liquid extract, dose, 15 to 60 min. and solid extract (1 to 5 grs.) are like bromides, believed to be sexual sedative and prescribed for nocturnal emission, masturbation, gonorrhoea and ovarian pain.

CHLORAL GROUP

1. CHLORALIS HYDRAS (*Chloral. Hydr.*), Chloral Hydrate, $\text{CCl}_3\text{CH}(\text{OH})_2$.

Chloral hydrate is prepared by saturating ethylic alcohol with dry chlorine and then adding water. Colourless, non-deliquescent, monoclinic plates, having a sharp pungent smell and bitter taste, slowly volatilising on exposure to air : contains not less than 99% of $\text{C}_2\text{H}_3\text{O}_2\text{Cl}_3$.

It is freely soluble in water at 15.5° , alcohol (90%) and solvent ether : liquefies when rubbed with the same quantity of camphor.

Dose, 5 to 30 grains or 0.3 to 2 grammes.

INCOMPATIBLES.—All alkalis decompose it liberating chloroform. With alcohol, it forms chloral alcoholate, not very toxic : with camphor, menthol, thymol, phenol, salol and novocaine, it forms a pasty mass.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, it is an irritant to the skin producing redness and warmth : a slight initial burning sensation is followed by local anæsthesia. [It is sometimes used for relieving the pain of a carious tooth and of superficial neuralgia^{325, 326}]. It is also a powerful antiseptic. But these actions are not so important.

TAKEN INTERNALLY, in small doses, it is a carminative but in the dose it is used as a hypnotic, in concentrated solution it is a gastric irritant and unless taken well-diluted, it may cause nausea and even vomiting.

It is rapidly absorbed from the gastro-intestinal tract unchanged and carried to the central nervous system, taken up by the nerve cells and produces the specific sedative effect there.

Nervous System.—(i) Given in 15 to 30 grains doses, it causes cerebral depression, mild but prolonged and produces fairly rapidly a phenomenon resembling natural sleep, lasting for several hours. It is a reliable hypnotic³²⁷ and is not often followed by any disadvantageous after-effect as nausea, headache or drowsiness.

Unlike many other narcotics, there is usually no stage of motor excitement.

This is the first synthetic hypnotic prepared by Liebig (1832) and introduced by Lebreich (1869) about 20 years after the volatile anæsthetics.

(325) R

Chloral. Hydr.

Menthol

Phenol aa. 1

Camph. 3 (B.P.C.)

For a painful carious tooth.

(326) R

Chloral. Hydr.

Menthol

Thymol aa. 1

Camphora 3 (Westminister)

Paint for a painful nerve or a joint.

(327) R

Chloral. Hydr. gr. 10

Pot. Brom. gr. 15

Syr. Aurant. min. 60

Aq. Aneth. ad. fl. oz. 1

A good hypnotic.

In the usual medicinal dose, it is **not analgesic** so that pain, if any present, is not relieved.

(ii) *The spinal reflex* is not affected with a moderate dose of 15 grains. But larger doses as 45 to 60 grains depress it [and in 15 to 20 grains dose repeated, it is of some value in **spasmodic conditions** like tetanus, whooping cough and strychnine poisoning³²⁸. When there is difficulty in swallowing, 20 to 30 grains of it may be given per rectum³²⁹]. But it is not a very suitable anticonvulsant and there are other more useful and safer drugs for this purpose.

(iii) An even larger dose, as 60 grains, causes a stage of anæsthesia characterised by profound stupor, diminished excitability of the motor areas of the brain, depressed pain sense and diminished reflexes with muscular relaxation. With still larger doses, the patient passes into a stage of surgical anæsthesia. But as the margin of safety between this stage and one of medullary paralysis is not great, this drug is unsuitable to be used as such.

Circulation.—(i) With a single therapeutic dose, as 10 to 15 grains sufficient to produce hypnosis, there is *no definite circulatory effect*: the slowing of the heart and the lowering of blood pressure are not any greater than those of natural sleep; but several such doses may cause marked circulatory depression and prove dangerous.

(ii) With a fairly big dose, as 30 grains, it is a **circulatory depressant**, acting directly on the *heart muscle*, like chloroform, first on the auricles and then on the ventricles. It also depresses the *vaso-motor centre* and the muscle of the *arterial wall*. The result is that the heart is slowed, the blood vessels, especially of the skin, dilate, the cardiac output is lessened and the blood pressure falls.

Respiration.—With the usual therapeutic dose, the breathing is slowed as in natural sleep and response to CO₂ stimulation is normal. But bigger doses, as 60 to 90 grains, cause medullary paralysis and the respiration and circulation both fail, the former becoming slow, shallow and irregular. Death takes place from respiratory failure.

Temperature.—On account of diminished muscular activity and a certain amount of dilatation of the cutaneous blood vessels, the production of heat is lessened and its loss increased; so chloral hydrate is a mild **antipyretic**. This is more obvious with bigger doses.

(328) ℞
Chloral. Hydr. gr. 15
Pot. Brom. gr. 10
Tinct. Bellad. min. 5
Syrupus min. 60
Aq. Menth. Pip. ad. fl. oz. 1
For a spasmodic condition.

(329) ℞
Chloral. Hydr. gr. 20
Pot. Brom. gr. 30
Mucil. Amyl. fl. oz. 2
To be given per rectum.

Uterus.—Chloral is said to promote relaxation of the cervix in the first stage of labour without greatly lessening the normal uterine contractions [and this with bromides is commonly prescribed in the first stage of labour. This not only helps relaxation of the cervix but, by inducing sleep, gives rest to the fatigued expectant mother].

Metabolism.—With prolonged administration in big doses, like chloroform, it causes an increased protein destruction which is shown in the urine by increased nitrogen, phosphorus and sulphur, these products of protein destruction being less perfectly oxidised than normal. But these effects are not much pronounced.

If taken fairly frequently for a long time, chloral hydrate tends to lessen the viscosity of the blood, destroy the red and white corpuscles and to cause fatty degeneration of the heart muscles, blood vessels, liver and of the kidneys.

The action of chloral hydrate was thought to be due to liberation of chloroform by its decomposition. But this has been found incorrect as the tissue is never sufficiently alkaline to do so and no free chloroform has been detected.

Elimination.—Chloral hydrate is mostly changed into trichlorethyl alcohol, $\text{CCl}_3\cdot\text{CH}_2\text{OH}$; (this is however doubted): this combines with glycuronic acid in the liver to form urochloallic acid. It is excreted in the urine which becomes highly acid. This may irritate kidneys to cause nephritis. Glycuronic acid reduces Fehling solution. A part is excreted unchanged and a minute quantity is excreted into the stomach, responsible for vomiting which is sometimes associated.

Caution.—Chloral hydrate is contraindicated in gastric, hepatic, renal and in severe cardiac diseases.

TOXIC SYMPTOMS may follow on taking large doses: these are deep coma, cardiac weakness with fall in blood pressure: slow and feeble respiration and lowering of the temperature:

Treatment is gastric lavage and large doses of leptazol or nikethamide with oxygen-carbon dioxide inhalation.

SUMMARY.—*Externally*, chloral hydrate is an analgesic and *internally*, if concentrated, is a gastric irritant. When absorbed, it causes selective depression of the central nervous system causing *hypnosis*: in bigger doses, *muscular relaxation* even *coma*. In therapeutic doses, has no action on circulation and respiration but bigger doses cause depression of the myocardium and of the medullary centres causing death.

Non-official Preparations

SYRUPUS CHLORALIS.—Chloral hydrate 2, distilled water 2 and syrup to make 10. (10.9 grs. in 60 minims).

Dose, 30 to 120 minims.

BUTYL CHLORAL HYDRATE.—It is less popular than chloral hydrate as a hypnotic because it is less certain in its action.

It is, however, sometimes prescribed for neuralgia of the fifth nerve as it is believed to be analgesic and is given in 5 to 20 grains doses, repeated every three hours³³⁰. But the result is uncertain.

2. CHLORBUTOL (*Chlorbutol.*), Chlorbutanol, Chloretone, $\text{Cl}_3\text{C.C}(\text{CH}_3)_2\text{OH}$.

Chloral is trichloro-*tert.*-butyl alcohol with a variable amount of water of crystallisation. It is prepared by heating a mixture of acetone and chloroform with caustic potash. Colourless crystals with a camphoraceous odour and taste. Volatile at ordinary temperature.

Soluble at 15°5, in 125 parts of water : in 1 part of alcohol (90%) : in 10 of glycerin and volatile oils : readily soluble in solvent ether. Should be stocked in a well-closed phial.

Dose, 5 to 20 grains or 0.3 to 1.2 grammes.

Pharmacology [and Therapeutics]

This is a popular drug and is very frequently used.

APPLIED EXTERNALLY, it is a mild antiseptic [and is used as a preservative for the solution of adrenaline hydrochloride and similar other unstable preparations].

It is somewhat anæsthetic also, being depressant to the sensory nerve endings³³¹. [It is often used with menthol and other volatile oils, as nasal and throat sprays³³² and is sometimes used as a dusting powder³³³ in surgical dressings for painful sores.

It is also sometimes prescribed for nausea and vomiting³³⁴ and probably it acts both locally as well as on the vomiting centre after absorption].

TAKEN INTERNALLY.—Although it is not absorbed from the unbroken skin, it does so from the mucous membranes and raw surfaces. It depresses the cerebrum causing sleep. But it is much less powerful than chloral hydrate and probably less depressant also. [In 10 to 15 grains dose it is prescribed, for insomnia in patients not suffering from any pain ; may be given in cachets]. In small repeated doses, it is useful in hiccough, vomiting and whooping cough.

Non-official Preparation

CHLORALAMIDE, Chloral Formamide.—It is a safe hypnotic and is said to give a natural refreshing sleep without any after-effect and is said to

| | | |
|---------|--|---|
| (330) B | Butyl Chloral Hydras gr. 4 Gelseminin. Hydrochlor. | Chlorbutol gr. 15 Paraff. Liq. Lev. fl. oz. 1 Throat and nose spray |
| | gr. 1/200 | (333) B |
| | Glycer. Trag. q.s. Pil. For neuralgia. | Chlorbutol 23 Zinc. Oxid. 120 Talc. 90 |
| (331) B | Chlorbutol 2 Camphor 2 Ol. Cinnam. 1 Ol. Cajuput. 5 parts For carious tooth. | A dusting powder, (334) B |
| | | Chlorbutol gr. 2 Hydrarg. Subchlor. gr. 1 Lactosum gr. 5 |
| (332) B | Menthol gr. 5 | Pulv. One every half hour for bilious vomiting. |

be without any depressing action on the heart or respiration and is further believed not to cause any drug habit.

But it is much less certain in its action. It is insoluble and some samples of it are very much so and may not be absorbed. The action may be greatly delayed.

Dose, 15 to 45 grains or 1 to 3 grammes.

ETHYLATED COMPOUNDS

1. SULPHONAL, $C_7H_{16}S_2O_4$.

Colourless crystals or white powder with very little smell or taste, very sparingly soluble in water, prepared by the oxidation of the product of interaction of ethyl mercaptan and acetone. Soluble in 450 of water, in 80 of alcohol (90%), in 90 of solvent ether and 3 of chloroform.

Dose, 5 to 20 grains or 0.3 to 1.2 grammes.

TRIONAL (Not official) a white, crystalline powder or lustrous scales with no smell but slightly bitter taste. Soluble in 320 of water and in 12 of alcohol (90%).

Dose, 5 to 20 grains or 0.3 to 1.2 grammes.

Pharmacology [and Therapeutics]

Both Sulphonal and Trional are much less popular than the newer drugs of the barbituric group. Both these induce **sleep without depression** of the heart or of the medullary centre but *do not allay pain*. These are insoluble in water, the absorption is slow and uncertain and they take a long time to act. This is 4 to 5 hours and drowsiness may continue long, often upto the next day. Trional is more rapid in action.

[These have also been used to check nausea as sea-sickness but sulphonal is so slowly excreted that drowsiness may persist till the next day. These are given in hot milk or in capsules].

These in larger doses are slightly irritant to both stomach and kidneys. The **excretion is rather slow** and so liable to cause **cumulative poisoning**. The toxic symptoms are, a feeling of general weakness, mental and physical, and dyspepsia. Urine sometimes contains hæmatoporphyrin, a decomposition product of hæmoglobin, even after a single dose.

Dreams and nightmares may sometimes follow as **after-effect of hypnosis**. Big doses cause profound depression, relaxation of the sphincters, lowering of the temperature and respiratory failure. These are now seldom used.

2. BARBITURIC ACID PREPARATIONS.

These are many and their number is progressively increasing. The official preparations are barbitone, barbitone sodium, phenobarbitone, phenobarbitone sodium, methylphenobarbitone, hexobarbitone, hexobarbitone sodium, pentobarbitone sodium and thiopentone sodium.

(i) **Barbitonum** (*Barbiton.*). Malonurea, Barbital. Barbitone, Diethyl-barbituric acid, *Veronal*, $C_6H_{12}N_2O_3$.

Barbitone is 5 : 5 diethylbarbituric acid and prepared by the condensation of ethyl diethylmalonate with urea.

White crystalline powder without smell but with faintly bitter taste, soluble in 170 of water but more so in hot water and also in watery alkaline solutions.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

TABELLÆ BARBITONI (*Tab. Barbiton.*), See p. 56. Strength. 95 to 105% of barbitone.

Dose, the same as of barbitone. Each tablet contains, if not otherwise stated, 5 grains.

(ii) **Barbitonum Sodium** (*Barbiton. Sod.*).—Sodium Barbitone, *Medinal*, $\text{NaC}_5\text{H}_{11}\text{O}_3\text{N}_2$. Prepared by the interaction of barbitone and caustic soda. A white, inodorous, crystalline powder with a bitter taste, soluble in 6 of water and sparingly in alcohol (90%) but not in chloroform or solvent ether. It contains between 98 and 101% of $\text{C}_5\text{H}_{11}\text{O}_3\text{N}_2\text{Na}$.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

TABELLÆ BARBITONI SODII (*Tab. Barbiton. Sod.*), See p. 56. Strength, between 92 and 105% of sodium barbitone.

Dose, as of sodium barbitone.

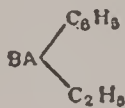
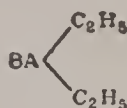
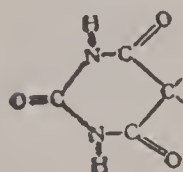
(iii) **Phenobarbitonum**.—Phenobarbitone, 5-Phenyl 5-ethylbarbituric acid : *Luminal*, *Gardenal*, $\text{C}_{12}\text{H}_{12}\text{O}_3\text{N}_2$.

Barbituric
Acid (BA)

Barbitone

Phenobar-
bitone

Prepared by the condensation of ethyl phenyl-ethylmalonate with urea. A white inodorous crystalline powder with a slightly bitter taste : soluble in 1000 part of water but freely in alcohol 90%, chloroform, solvent ether and in watery solution of alkali hydroxides and carbonates. Dose, $\frac{1}{2}$ to 2 grains or 30 to 120 mg.



TABELLÆ PHENOBARBITONI (*Tab. Phenobarbiton.*), See p. 57. Strength is 90 to 110% of phenobarbitone.

Dose, the same as of phenobarbitone.

(iv) **Phenobarbitonum Sodium** (*Phenobarbiton. Sod.*).—Soluble Phenobarbital. *Luminal Sodium*, $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}_2\text{Na}$.

Prepared by the interaction of phenobarbitone and caustic soda. An inodorous, white, hygroscopic powder with a slightly bitter taste. Very soluble in water and also in alcohol (90%), insoluble in chloroform and solvent ether.

Dose, $\frac{1}{2}$ to 2 grains or 30 to 120 mg. A single dose by intravenous or intramuscular injection, 1 to 3 grains or 60 to 200 mg.

INJECTIO PHENOBARBITONI SODII (*Inj. Phenobarbiton. Sod.*), See p. 46. The sealed container contains between 88 to 110% of the labelled amount of sodium phenobarbitone.

Dose, sodium phenobarbitone, single administration, 1 to 3 grains or 60 to 200 mg. by intramuscular or intravenous injection.

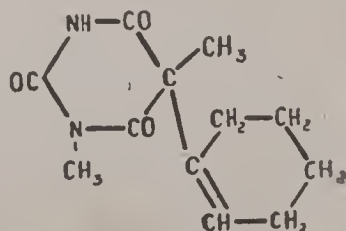
TABELLÆ PHENOBARBITONI SODII (*Tab. Phenobarbiton. Sod.*), See p. 57. Should be in a well-closed container.

Dose, the same as of soluble phenobarbitone.

(v) **Hexobarbitonum**, Hexobarbitone, Hexobarbital, $\text{C}_{12}\text{H}_{16}\text{O}_3\text{N}_2$, is 5- Δ^1 -cyclohexenyl-5-methyl-N-methyl-barbituric acid, obtained by condensation of methyl- Δ^1 -cyclohexenyl methylcyanoacetate with methyl urea, followed by hydrolysis of the product.

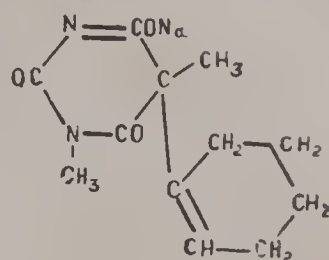
Colourless, odourless prismatic crystals, soluble in about 3000 parts of water at 20° : soluble in dehydrated alcohol, methyl alcohol, acetone, benzene, chloroform and in solvent ether.

Dose, 4 to 8 grains or 0.25 to 0.5 gramme.



(vi) **Hexobarbitonum Sodium** (*Hexobarbiton. Sod.*), soluble hexobarbitone, $C_{12}H_{13}O_3N_2Na$. *Evipan Sodium*, is monosodium salt of the above prepared by its interaction with sodium hydroxide. It contains between 98 to 101% of $C_{12}H_{13}O_3N_2Na$, the substance being dried at 100° .

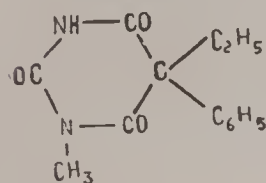
A white inodorous, very hygroscopic powder with a bitter taste. Very soluble in water, alcohol, methyl alcohol and in acetone: slightly soluble in chloroform and solvent ether. An aqueous solution absorbs CO_2 , hexobarbitone crystals separating.



Dose, 3 to 15 grains or 0.2 to 1 gramme intravenously or intramuscularly and 30 to 60 grains or 2 to 4 grammes per rectum.

INJECTIO HEXOBARBITONI SODII (*Inj. Hexobarbiton. Sod.*). See p. 44. The sealed container should contain between 88 to 110% of the labelled amount of sodium hexobarbitone.

(vii) **Methylphenobarbitonum**, *Phemitone*, *Prominal*, $C_{13}H_{14}O_3N_2$ is N-methyl-5-phenyl-5-ethylbarbituric acid, may be obtained by condensing diethylphenyl ethylmalonate with methyl urea.



White crystalline, inodorous and tasteless powder, almost insoluble in water, soluble in alcohol 90%, solvent ether, chloroform and in watery solution of alkali hydroxide.

Dose, 1 to 3 grains or 60 to 200 mg.

(viii) **Pentobarbitonum Sodium** (*Pentobarbital Sodium*), Soluble pentobarbitone, *Nembutal*, $C_{11}H_{11}O_3N_2Na$ is the monosodium derivative of 5-ethyl 5-(1 methyl butyl) barbituric acid.

Prepared by the interaction of this substance and sodium ethoxide contains between 98.5 to 101% of $C_{11}H_{11}O_3N_2Na$, dried at 90° .

A white crystalline powder or granules, inodorous with slightly bitter taste. Freely soluble in water and alcohol, nearly insoluble in ether. This should be stored in a well closed container.

Dose, $1\frac{1}{2}$ to 3 grains or 0.1 to 0.2 gramme.

(ix) **Thiopentonium Sodium** (*Thiopent. Sod.*), soluble thiopentone, *Pentothal sodium* is a mixture of monosodium derivative of 5-ethyl-5-(1-methylbutyl)-thiobarbituric acid 100 and exsicc. sod. carb. 6.

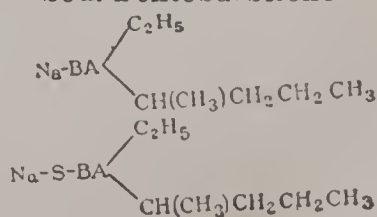
A yellowish white, hygroscopic powder with slight alliaceous odour and bitter taste. Soluble in water, partially in alcohol but insoluble in solvent ether and in benzene.

Dose, $1\frac{1}{2}$ to 8 grains or 0.1 to 0.5 gramme by intravenous injection.

INJECTIO THIOPENTONI SODII (*Inj. Thiopent. Sod.*), See p. 48. Sodium thiopentone content in each should be between 90 and 110% of the labelled amount.

Dose as of sodium thiopentone.

Sod. Pentobarbitone



Sod. Thiopentone

Pharmacology [and Therapeutics]

Veronal (Fischer and Mering, 1903) or barbitone and several other hypnotics prepared from or allied to barbituric acid are now getting increasingly popular so much so that the number exceeds several hundreds.

Barbituric acid is a combination of urea and malonic acid. To the end carbon an ethyl group added forms *barbitone*. By

replacing one or both of the ethyl group by ether alkyl, aryl or complex cyclic radicals, many other compounds have been formed. Addition of a phenyl group to the end carbon makes *phenobarbitone* and gives the property of lessening the cortical motor activity : that of complex cyclic radical causes diminished stability and increased destruction in the body as in *evipan*. These compounds forming salts as with sodium become freely soluble in water.

GENERAL ACTIONS.—Barbitone preparations are depressant to the central nervous system and are used to cause *calmness* (sedation) and *sleep* : *to stop convulsion* and cause partial or complete *anæsthesia*.

The *advantages* are : (a) these are fairly certain in action ; (b) have selective depressant action on the central nervous but not so much on the cardio-vascular systems ; (c) can be taken for a long time with comparatively few toxic symptoms ; (d) their dose is small, have no disagreeable taste and do not cause any gastro-intestinal disturbance. Price is moderate.

These act mostly on the *brain-stem* near the thalamic areas ; some act on the *cortex* and the *spinal cord* also.

In therapeutic doses, these have no action on the gastro-intestinal tract, liver, kidneys, respiration or on the circulation. Large doses cause relaxation of intestinal muscles, diminished urination, lessening of respiratory movements, vaso-dilatation and fall in blood pressure. Metabolism and body temperature may be slightly diminished. A toxic dose causes death from depression of the respiratory centre.

ELIMINATION AND DESTRUCTION.—Several of these are oxidised in the liver and these have shorter action and are suitable for basal anæsthesia. *Evipan* and *pentothal sodium* are readily destroyed in the liver. Others as *pentobarbital*, *amytal* and *ortal* are partially destroyed. *Barbital*, *phenobarbital* and *dial* are mostly eliminated by the kidneys. The importance of kidney elimination (slow) and destruction by the liver (rapid) lies mainly in the duration of the action and possibilities of cumulative poisoning.

The barbiturates greatly vary in their action regarding the rapidity of *onset*, and the *duration* : those taking a longer time to be effective have greater duration.

(i) *Slowly acting barbiturates* : *barbitone*, *phenobarbitone* and *methylphenobarbitone*. *Barbitone* is used as hypnotic but drowsiness tends to continue till the next day ("hang-over" phenomena) : *phenobarbitone* is even slower in effect with more prolonged action and is suitable for use as anticonvulsant and *methyl phenobarbitone* is used as anticonvulsant only.

(ii) *Intermediate action* : *allobarbitone (dial)*, *butobarbitone (soneryl)* and *amylobarbitone (amytal)* are suitable hypnotics, the action starting in half hour and extends to 4 or 5 hours, thus causing no "hang-over" phenomena.

(iii) *Short-acting barbiturates* : pentobarbitone (*nembutal*) and cyclobarbitone (*phenodorm*) cause quick hypnosis and are useful in persons who once made asleep, may continue : also useful for pre-anæsthetic sedation.

(iv) *Very short-acting barbiturates* : hexobarbitone (*evipan*) and thiopentone are rapidly acting intravenous anæsthetics used for short operations and as pre-anæsthetic medication.

IDIOSYNCRASY AND TOLERANCE.—In some persons narcosis persists longer ("hang-over" phenomena) : in others, there may be allergic manifestations as urticaria or asthma (these readily pass off).

No marked tolerance is established. No obvious drug habit is formed except with pentobarbitone and amytal : some patient may have symptoms when the drug is suddenly stopped.

THERAPEUTIC USES.—These are (i) for **sedation** and for **hypnosis**. A slowly eliminated drug is chosen : this causes sleep for 4 to 6 hours. As the induction is slow and hang-over effect may be produced in some persons, in them a more rapidly acting drug as seconal, amytal, ortal or pentobarbitone may be used. Usually one dose is given for *hypnosis* but several much smaller doses are required for *sedation* in a condition of persistent mental excitement.

(ii) As **anticonvulsant**, cortical depressant as phenobarbitone and methylphenobarbitone (*prominal*) are useful for repeated administration for many months or years as in epilepsy. For rapid action in emergency, evipan, pentobarbitone or pentothal sodium may be used per rectum, intramuscularly or intravenously.

[Other anti-convulsants as *bromides* and *chloral hydrate* are less powerful, whereas *diphenylhydantoin sodium* and *mesantoin* are more powerful].

(iii) As **anæsthetic**, basal narcotic or for lessening labour pain at the point of delivery, intravenous administration of sodium evipan, sodium pentobarbital or sodium pentothal are suitable : harmless anæsthesia of a short duration is obtained.

(iv) As **analgesic**, these themselves are not very effective but in combination with coal-tar analgesics these are so. The effects are intensified : a combination of barbiturates with amidopyrine (as in *veramon* or *allonal*) is a powerful analgesic. (See p. 499).

These should be used with caution in gross renal and hepatic diseases.

(1) **BARBITONE** (*Veronal*) and **SODIUM BARBITONE** (*Medinal*) are quickly absorbed. Given in a therapeutic dose, 5 to 10 grains, these accumulate largely in the thalamic region of the brain. Sleep follows in 1 to 2 hours like natural sleep which lasts for several hours **without depression** of the circulation. These are, however, **slowly excreted** and if the dose is large, drowsiness, headache and dizziness may persist till the following day. In some cases, the sleep is dreamy and unrefreshing and at times, particularly in old people, drowsiness many persist for even

24 to 36 hours. If continued fairly long, these may cause chronic **cumulative poisoning**. Weakness, mental and physical instability and tremors appear. In other cases, erythematous skin eruptions, cyanosis, mental aberration and ataxy are seen. These are **habit-forming** also.

The excretion is mainly by the kidneys, only a part is oxidised in the liver.

Acute poisoning is also sometimes seen when a big dose as 40 to 50 grains is taken especially for suicidal purpose. The symptoms are of profound mental depression and stupor with feeble respiration and lowered body temperature. Death takes place from respiratory failure usually taking more than 24 hours.

The stomach should be immediately washed out. Leptazol, caffeine and picrotoxin in big (convulsive) doses have been found antidote to profound narcosis of barbiturates. Intravenous drip of dextrose-saline is also necessary.

(2) **PHENOBARBITAL** (*Luminal*), resembles barbitone, as only one of the ethyl groups is replaced by a phenyl group. It has a similar action and used as **hypnotic**³³⁵ but is more effective in **lessening motor activities** (cortico-motor depression). [It was prescribed for **epilepsy**³³⁶ in 2 to 4 grains doses, more or less continuously for several months, till the fits disappear. After this the dose may be gradually lessened]. It sometimes manifests *idiosyncrasy*: skin eruptions with itching, slight rise of temperature, gastric irritation, diplopia, vertigo and disturbances of speech are occasionally seen (Cushny) and is now not so much used.

It is also used in small repeated doses for **sedation** as in pylorospasm, chorea, whooping cough, asthma or in hyperthyroidism.

The drug is mainly eliminated by the kidneys and partly oxidised in the body.

SOLUBLE PHENOBARBITAL (sodium gardenal or sodium luminal) is sometimes given for the same purpose orally³³⁷ and more often hypodermically in 20% solution (available in 1 c.c. ampoule, each containing 3 grains) for mental excitement as following cocaine poisoning, delirium tremens or for a **convulsive state** [as of strychnine poisoning, eclampsia and tetanus].

Intravenous injection for basal narcosis is not sufficiently safe. A dose of one of these may, however, be given orally for **pre-anæsthetic nervousness**³³⁸.

- (335) R
Luminal gr. 1
Chlorbutol gr. 10
Lactosum gr. 10
Pulv. A hypnotic.
- (336) R
Luminal gr. 1½
Calc. Glucon. gr. 10
Pulv. For epilepsy.

- (337) R
Luminal gr. ¼
Chlorbutol gr. 1
Lactosum gr. 5
Pulv. Every hour for vomiting.
- (338) R
Phenobarbiton. Solub. gr. 1
Pot. Brom. gr. 10
Aq. Chlorof. fl. oz. 1
Nerve sedative.

AVAILABLE as *Gardenal* and *Gardenal sodium* tablets of $\frac{1}{2}$, 1 and $1\frac{1}{2}$ grains : ampoules 1 c.c. has 3 gr. of gardenal sodium, also *luminal* and *luminal sodium* of similar strength.

(3) METHYL PHENOBARBITONE has recently attained popularity for treatment of **epilepsy** given in 2 to 3 grains doses 2 to 3 times daily ; "the fit rate" is markedly reduced and the drug may be continued for several years without causing mental deterioration or sleepiness.

May be used as RUTONAL (Methophenobarbitone), $\frac{1}{2}$ gr. and 3 gr. tablets.

(4) HEXOBARBITONE (*Evipan*) may be used as a **hypnotic** (4 gr. tablets) and more often as **pre-anæsthetic medication** to avoid the anxieties and excitements during the administration of a volatile anæsthetic.

Soluble hexobarbitone (evipan sodium) in sterile ampoule of 0.5 to 1 gramme in freshly made 10% solution is given intravenously very slowly as a **full surgical anæsthetic**, or as **basal anæsthetic**. (a) Usually 2 to 3 ml. is given intravenously in 10 to 15 seconds : this causes **general anæsthesia** for 2 to 3 minutes, sufficient for a short operation as extraction of a tooth or incision of an abscess : further doses of 1 ml. in 15 seconds may be given for a greater depth of anæsthesia and 10 ml. in all should be considered the maximum limit. It is not however quite safe to go as far as this for complete surgical anæsthesia because the effect of an overdose cannot readily be counteracted. The injection should be given in *recumbent position* as there is the risk of syncope. It is especially contraindicated if hepatic, respiratory and cardiac diseases are present. It sometimes causes clonic muscular movements.

(b) It is admirably suited for **basal anæsthesia** in 3 ml. dose, the patient becoming unconscious in 2 minutes : not only the patient takes a volatile anæsthetic more comfortably and safely, post-operative pain and excitement are also controlled. The recovery is fairly rapid as the drug is oxidised very quickly.

(c) It is also sometimes prescribed for severe **uncontrollable convulsive attacks** : may be given intravenously, intramuscularly or per rectum (for the last, about 2 gram. may be tolerated).

AVAILABLE as *Cyclonal* tablets (0.25 g.) oral and *Cyclonal sodium* ampoules 0.5 g. and 1 g. dry (to be dissolved immediately before use in 5 or 10 c.c. of sterile water).

Toxic effects are fall in blood pressure and respiratory depression. Intravenous injection of nikethamide 5 c.c. or 5 mg. of picrotoxin should be immediately given and repeated every 30 minutes. Amphetamine sulphate orally and if comatose, intravenously (20 mg. every $\frac{1}{2}$ to 1 hour) may be necessary if picrotoxin causes muscular twitchings.

(5) PENTOBARBITAL is a safe **hypnotic** acting with a small dose, as 1 to 2 grains, sleep coming rapidly which is not unduly prolonged as the drug is slowly destroyed by the liver. To minimize **labour pains**, $1\frac{1}{2}$ gr. is given when labour commences

and repeated when necessary upto the maximum of 8 gr. In old persons, it may occasionally cause excitement.

PENTOBARBITONE SODIUM, *Nembutal* in $1\frac{1}{2}$ grs. capsule by mouth for hypnosis or as pre-anæsthetic medication and $7\frac{1}{2}$ grs. in 10 c.c. ampoule, is given intravenously at the rate of 1 c.c. per minute for basal anæsthesia or to stop convulsion. The action is fairly rapid and as the elimination is also equally so, there is usually no toxic symptom.

DANGERS are of *respiratory depression* and post-operative pneumonia. Prolonged administration may cause *skin lesion* and *liver damage*.

(6) SOLUBLE THIOPENTONE, Pentothal Sodium.—This is given orally in $1\frac{1}{2}$ to $2\frac{1}{2}$ grain doses or intravenously in 5% solution, 2 to 3 c.c. and repeated. Morphine-atropine injection is also often given 45 minutes before.

This is probably the most powerful barbiturate and as safe as evipan. Induction of anæsthesia is pleasant without muscular twitchings which may be present with evipan. Muscular relaxation is good. Toxic effects as respiratory depression, fall in blood pressure or post-anæsthetic headache and vomiting are rare. Anæsthesia is rapidly induced and rapidly recovered from and very suitable for a short operation.

AVAILABLE as *Intraval sodium* ampoules of 0.5 and 1 g. dissolved in 10 and 20 c.c. of sterile water.

COMMERCIAL PREPARATIONS

AMYTAL, amylobarbitone, in $1\frac{1}{2}$ gr. tablets, is given orally as hypnotic and 3 grs. for pre-anæsthetic nervousness.

It is also given for bronchial asthma in combination with ephedrine as a central sedative.

SODIUM AMYTAL, 1 g. (15 grs.) 10 c.c. in ampoule is given intravenously at the rate of 1 c.c. per minute for basal anæsthesia. In a few cases there is a stage of excitement and always some lowering of the blood pressure, respiratory rate and body temperature. It should not be given to debilitated persons.

SECONAL (Sodium propyl methyl carbinyllallyl barbiturate) is a quick acting short staying hypnotic: $1\frac{1}{2}$ gr. capsule, 1 or 2, as hypnotic: 2 or 3 as postoperative medication or in the first stage of labour.

ORTAL SODIUM, sodium-n-hexylethyl barbiturate tablet, is hypnotic (0.2 to 0.4 g.).

PHANODORM, Cyclobarbitone in 3 gr. tablets causes quick short-lived hypnosis and no after effect.

PERNOCTON, in 10% solution is given intravenously at the rate of 1 c.c. per minute for basal anæsthesia: said not to cause any fall in blood pressure nor any excitement.

For an operation requiring a fairly long time, N₂O and oxygen or ether may also be given with the above.

SOMNIFAINE, oral liquid 20 to 60 drops and ampoule 2.2 c.c. intramuscularly, is anticonvulsant and hypnotic.

NIRVANOL, has been found useful in chorea although continued for over a week it may cause a skin rash along with fever.

SONERYL (butyl-ethyl barbituric acid) tablet of $1\frac{1}{2}$ gr. and capsules of soneryl sodium $2\frac{1}{4}$ gr. are also similarly used as hypnotic and sedative to motor system.

SONALGIN, soneryl 1 gr., codeine phosph. $\frac{1}{6}$ gr. and phenacetin $3\frac{1}{2}$ gr. in each. Analgesic and hypnotic.

VERAMON, amidopyrine diethyl-barbiturate, in 6 grs. tablets is used as analgesic hypnotic.

ALLONAL is a combination of barbiturate with amidopyrine; 1 to 4 tablet daily for analgesia and hypnosis.

SANDOPTAL, isobutylallylbarbituric acid, in 0.2 g. tablet: hypnotic of moderate strength.

OPTALIDON (Sandoptal, amidopyrine and caffeine), pill, analgesic without being hypnotic.

DIAL, diallylbarbituric acid in tablet and ampoules is a hypnotic and CIBALGIN, dial with amidopyrine in tablets and 2 c.c. ampoules, is analgesic.

DIDIAL, diallyl barbiturate of ethyl morphine $\frac{1}{2}$ gr. and dial $1\frac{1}{2}$ gr. in tablet is analgesic-hypnotic.

CARBROMALUM, Uradal, Adalin, α -bromo- α -ethylbutyryl carbamide with urea in 5 gr. tablets, 2 such, given in cases for mild hypnosis.

CARBITAL contains pentobarbital sodium $1\frac{1}{2}$ gr. and carbromal 4 gr. in tablet. Rapidly acting hypnotic.

SEDORMID, allylisopropylacetyl carbamide in 4 gr. tablet is hypnotic and sedative.

3. URETHANUM (*Urethan.*), Urethane, $\text{NH}_2\text{CO.OCH}_2\text{H}_5$.

Urethane or ethyl carbamate is prepared by the action of ammonia on ethyl chloroformate.

Colourless, prismatic inodorous crystals or leaflets with cooling, saline and slightly bitter taste: soluble in water at 15.5° in 2 parts, in alcohol 90%, solvent ether, chloroform, glycerin and in fixed oils, 1 part.

Dose, 15 to 30 grains or 1 to 2 grammes.

Injectio Quininæ et Urethanæ (*Inj. Quinin. et Urethan.*), See p. 46. Dose, 8 to 75 minims or 0.5 to 5 ml. intravenously as a sclerosing agent.

Urethane is a mild hypnotic especially in children causing light sleep without after effects: advantage is that it is not much depressant. Sometimes it fails to act. It is changed in the system into and excreted as urea causing slight diuresis.

It is a more powerful hypnotic in animals and hence is often used in the laboratory in animal experiments: blood pressure and respiration are unaffected and normal reflexes remain unchanged.

Injected subcutaneously, it is an anæsthetic of moderate intensity. It is used with quinine hydrochloride as a sclerosing agent for varicose veins.

Urethane has been used in the treatment of myeloid leukæmia, lymphogranulomatosis and multiple myeloma. The benefit is due to destruction of maturing segmenting leucocytes. Dose to start with is 0.5 g. (8 grains) slowly increased to 6 g.

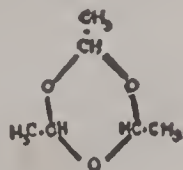
Signs of intolerance are nausea and vomiting and progressive anæmia (toxic depression of bone marrow).

ALDEHYDE

PARALDEHYDUM (*Paraldehyd.*), Paraldehyde, $\text{C}_6\text{H}_{12}\text{O}_3$.

A colourless, transparent liquid of a peculiar odour and a burning taste, prepared by the polymerisation of acetaldehyde. A suitable antioxidant, 0.01% w/v may be added. It should be stocked away from light and air. Soluble 1 in 9 of water and freely in alcohol (90%), solvent ether, chloroform and volatile oils.

Dose, 30 to 120 minims or 2 to 8 ml. orally: per rectum as a basal anæsthetic, $\frac{1}{2}$ to 1 fluid ounce or 15 to 30 ml.



Pharmacology [and Therapeutics]

Paraldehyde is rapidly absorbed from the gastro-intestinal tract and its characteristic odour is obtained in the breath in a few minutes.

(i) Paraldehyde is a **safe hypnotic** as it does not cause any cardiac depression and it may be given to patients suffering from heart disease³³⁹. It is fairly certain in its action and taken at bed time, sleep following quickly in 15 to 20 minutes, lasts for several hours with no after-effects. Even with a big dose, often no greater harm is done than prolonged unconsciousness and muscular relaxation due to the depression of the anterior horn cells of the spinal cord. It is especially useful in mental and heart diseases: also in a acute febrile state.

But it has a **disagreeable smell** which remains in the breath till the next morning. It is therefore not liked by patients. It may however be taken with milk, fruit juice or in crushed ice. As it resembles alcohol, it may, especially if given in a small dose, cause intoxication with *excitement*. If frequently repeated, it may cause erythematous *rash*: less commonly, a *drug habit*.

(ii) It is given per rectum, 15 to 30 c.c., in milk, olive oil or in normal saline (as a local anæsthetic, 1 c.c. benzyl alcohol may be added) in 10% solution, as a **basal narcotic**, one hour before the administration of a volatile anæsthetic. The unpleasant stage of excitement and mental shock are avoided.

(iii) For convulsive state, unrelieved pain of coronary thrombosis and for obstetrical analgesia to lessen labour pain, paraldehyde may be given per rectum.

Excretion.—Paraldehyde is largely destroyed in the liver, partly escapes through the lungs and only a small amount through the kidneys. So it is not contraindicated in diseases of the kidneys but it is unsuitable in chronic hepatic and pulmonary diseases.

A certain amount of **tolerance** may be acquired by taking it repeatedly but its disagreeable odour is a protection against frequent use.

CHOICE OF HYPNOTICS

(i) When wakefulness is due to nervous excitement, *bromide* is indicated. *Chloral* is more powerful, has rapid action and is fairly safe also unless fatty changes are present in the heart muscles. *Barbitone* and *phenobarbitone* are comparatively

(339) B
 Paraldehydum
 Ext. Glycyrrh. Liq. aa. min. 60
 Syr. Acac. min. 120
 Aq. Menth. Pip. ad. fl. oz. 2
 A safe hypnotic.

ANTICONVULSANTS

slowly acting : these in combination with chlorbutal suitable and the action lasts for 5 to 6 hours. *nembutal*, *seconal* and *soneryl* are more rapidly acting the action may be short-staying. *Adalin* is also satisfactory as a mild hypnotic. *Paraldehyde* is rapidly acting and is safe but the disadvantage is its smell which tends to hang on for several hours. *Opium alkaloids* (especially morphine) are used only if pain is the cause of sleeplessness : the effect is prompt and very satisfactory. Sleeplessness with slight pain may yield to *veramon*, *allonal*, *didial* or *veganin*.

(ii) For *Sedation*, bromide-chloral-valerian mixture (p. 132) or phenobarbital $\frac{1}{2}$ to 1 gr. (30 to 60 mg.) may be given 2 to 3 times daily.

IV. ANTICONVULSANTS

Drugs with depressant action on the motor cells of the central nervous system are used as **anticonvulsants**. (1) Sudden severe convulsion of prolonged nature requires such powerful sedatives as chloral hydrate and paraldehyde or bromethal per rectum : chloroform by inhalation and anæsthetic barbiturates as sodium salts of hexobarbitone, pentobarbitone and thiopentone by intravenous injection.

(2) In other cases, fits of varying severity are repeated at certain intervals : these are best seen in epilepsy.

Drugs chosen are continued fairly long as sudden stopping of further administration may bring in a relapse. One to be suitable for prolonged administration, (a) should be without cumulative toxic effects : (b) should have limited specific action on the motor cells only without being hypnotic and (c) should cause no mental depression or destruction of the brain cells. An ideal preparation is difficult to find.

(i) For many years, *bromides* were the only dependable drugs. These if continued long, caused fetid breath, mental depression and skin rashes.

(ii) These were partly replaced by *phenobarbitone*, (*luminal*) and *methyl phenobarbitone* (*prominal*) : of these, the last is a more active motor depressant than hypnotic. Major epilepsy (*grand mal*) responds better than minor epilepsy (*petit mal*). Effects are produced in 2 or 3 days.

The optimal dose is determined by giving a phenobarbitone in slowly increasing doses ; this is started with 0.1 g. daily and increased till the fits are controlled, either in several divided doses or in one big dose at bed time for nocturnal fits and in the morning for diurnal type. The total dose may be 0.2 or 0.3 g. or more. If this causes drowsiness, dizziness, ataxia and psychosis, benzedrine (5 to 25 mg. daily) may be given along with it.

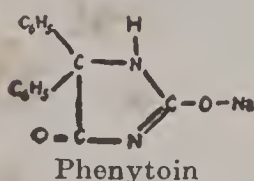
When the proper therapeutic effect is produced, the dose is slowly reduced but the drug should never be suddenly stopped.

Disadvantages are cumulative poisoning and occasionally mental deficiency.

(iii) Recently *Phenytoin sodium* has been found more useful.

(iv) Drugs of even more recent introduction are Methyl-phenyl-ethyl-hydantoin (*Mesantoin*), Trimethyl oxazolidine dione (*Tridione*) and *Mebaral*.

PHENYTOINUM SODIUM (*Phenytoin. Sod.*), Soluble Phenytoin, Diphenylhydantoin Sodium, $C_{15}H_{11}O_2N_2Na$.



Phenytoin sodium is monosodium derivative of 5 : 5-diphenyl-hydantoin, prepared by heating diphenyl-bromo-acetylurea with alcoholic ammonia and treating with sodium hydroxide. Contains between 98 to 101% of $C_{15}H_{11}O_2N_2Na$ of the substance dried at 100° .

A white inodorous powder, moderately hygroscopic ; on exposure to air, CO_2 is absorbed liberating diphenylhydantoin.

Freely soluble in water making a turbid solution due to hydrolysis. Soluble in alcohol (95%) but not in solvent ether or chloroform.

Dose, $\frac{2}{3}$ to $1\frac{1}{2}$ grains or 50 to 100 mg.

Pharmacology [and Therapeutics]

Phenytoin sodium (*Dilantin sodium*) given by the mouth raises the **threshold of cortico-motor excitability** in animals without hypnosis : this by direct electrical stimulation has been found to be raised two to four times whereas sodium bromide can raise it not above 50%. Phenobarbitone to raise this threshold 2 to 4 times, would cause profound hypnosis.

Given therapeutically to an epileptic suffering from *major fits* (**grand mal**) in 0.1 g. doses 3 or 4 times daily, it gradually lessens the number and intensity of the fits. Further, the mental condition especially if made torpid by bromide or barbitone medication, remarkably improves : the patient becomes more alert with better mental concentration and memory. **Psychomotor equivalent attacks** also improve. These indicate that dilantin sodium acts on the motor cortex and other higher cerebral centres.

The action in most cases is probably *symptomatic suppression* of fits without correction of pathological dysrhythmia responsible for epilepsy.

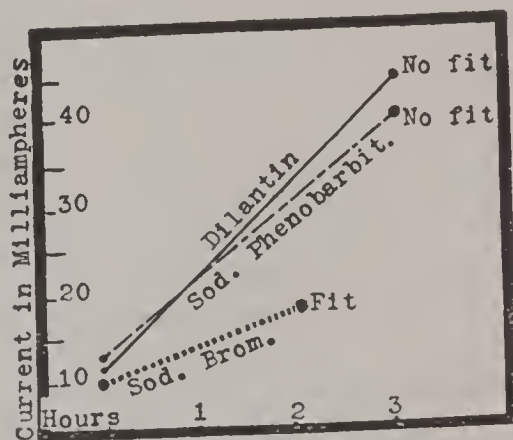
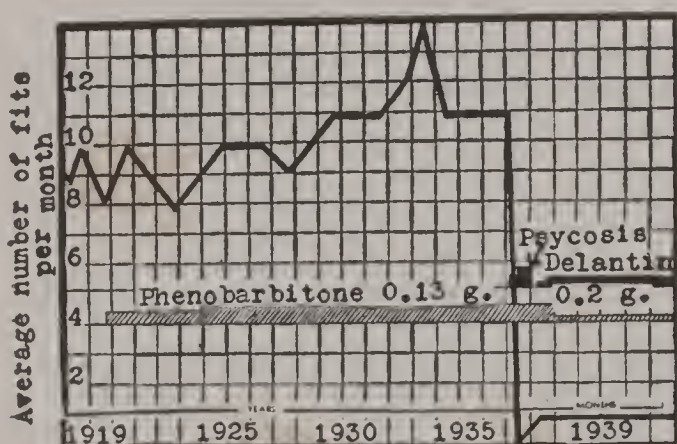


Fig 26.—Comparative increase of "fit-threshold" by therapeutic dose of sodium bromide, phenobarbitone and dilantin.

The drug absorbed is mostly destroyed or altered in the body and only a small fraction is eliminated in the urine.

THERAPEUTIC USE.—As the action of phenytoin sodium takes a few days to manifest fully, if the patient is already on phenobarbitone (phenytoin is chemically related to phenylethylbarbituric acid), it is not immediately stopped and is continued in the previous dose and 0.1 g. of phenytoin added once daily: this dose is doubled on the 4th to the 7th day: on the 8th day, increased to 0.3 g. and phenobarbitone



(Lennox)

Fig. 27.—The comparative effects of phenobarbitone and dilantin sodium in a case of epilepsy.

is progressively lessened or stopped. The maximum dose of phenytoin may be 0.6 g. daily. If the patient was not previously under treatment, the starting dose may be 0.1 g. 3 times daily and gradually increased to full dose of 0.6 g. daily. Children of 6 years and over may commence with 0.1 g. dose and maximum is 0.4 g. If below 4 years, 30 mg. should be the starting dose. It should be continued for many months or years. Dose in excess of what will prevent convulsion should not be given.

The drug is strongly alkaline (pH 11) and hence is dispensed in capsules or pills of 0.1 g. To young children it is given in cream.

Merrit and Putnam (1938) first reported the successful clinical results which were subsequently corroborated by many other observers. It has been found that phenytoin is of less value in petit mal (minor epilepsy) and in about 15% of cases causes toxic symptoms. Even in major fits, combined treatment with phenobarbitone sometimes gives better result.

Toxic Symptoms.—These are often *mild* and the treatment may be continued in a little smaller dose. If *severe*, the treatment has to be temporarily suspended.

(i) *Central nervous system*.—There may be rise in temperature, giddiness, ataxia, nervousness, tremors, irritability, nystagmus, diplopia, ptosis, psychosis, paræsthesia and even status epilepticus.

(ii) *Gastro-intestinal system*.—Nausea, vomiting, abdominal pain and tender and hyperplastic gums.

(iii) *Skin*.—Eruptions, erythematous, morbiliform or scarlatinal (appear from the 7th to the 15th day), very rarely purpura or exfoliative dermatitis.

AVAILABLE as *Dilantin Sodium*, *Epanutin*, *Eptoin* and *Solantoin* in capsules or pills.

Non-official Preparations

(i) MESANTOIN, methyl-phenyl-hydantoin, recently introduced causes (a) less toxic symptoms especially the nervous symptoms, gastric irritation and gum hyperplasia but may occasionally cause fever and skin eruptions. (b) The anticonvulsant action is claimed to be better.

Dose.—Commenced with 0.05 g. ($\frac{1}{2}$ tablet) daily and increasing at weekly intervals by 0.05 g. : at the end of the 2nd month, 0.4 to 0.6 g. (4 to 6 tablets) are reached and this dose is maintained till the fits are effectively controlled and then the dose may be gradually reduced. If the patient is already under treatment with another anticonvulsant, its dose should be gradually reduced.

Toxic Symptoms as appearance of morbiliform skin rash may require reduction of the dose, phenobarbitone being added to keep up adequate sedation. In fact, mesantoin may be given along with phenytoin and phenobarbitone.

(ii) TRIDIONE, 3, 5, 5-trimethyloxazolidine-2, 4-dione available in 0.32 gm. capsules, 1 to 2 gm. daily, has been found useful in petit mal and myoclonic and akinetic epilepsy.

Toxic Symptoms are skin rashes and unusual sensitivity to bright light.

SUMMARY.—The anticonvulsant drugs for major epilepsy should have selective depression of the cortico-motor area which if continued long, should not cause mental and physical deterioration or undue sleepiness. Bromides, phenobarbitone and methyl phenobarbitone were successive stages of improvement. Phenytoin has better sedative effect but may cause toxic symptoms. Mesantoin is equally sedative but less toxic. For minor epilepsy, tridione is promising.

V. NARCOTICS

NARCOTICS are usually meant to represent a group of drugs which are taken for a pleasant sensation of partial depression and partial excitement. A tolerance is soon established requiring a gradually increasing dose so that a habit is formed and there is craving for repeated indulgence. With bigger doses, these cause sleep which deepens into coma, more profound than that of a usual hypnotic.

The important drugs of this group are *alcohols*, *opium*, *cocaine* and *cannabis indica*. The drugs of the *belladonna* group in big doses also act as narcotic and produce deep coma but these are more commonly used as stupefier for criminal purposes than for habitual drug indulgence. Hyoscine is used as hypnotic only.

OPIUM (*Opium*), Raw opium, *Ahifen*

Opium is the juice, (*G. Opos*, sap), obtained by incising the unripe white poppy capsules of *Papaver somniferum*, which is subsequently thickened by gradual evaporation. It is a blackish brown mass with a peculiar strong smell and bitter taste. It must contain at least 9½% of anhydrous morphine : if it contains more than 10%, it should be diluted with opium of lesser strength or with sugar of milk.

Opium is of four varieties : (i) *Indian*, medicinal and commercial, (ii) *Turkey*, "soft shipping" containing 30% moisture and a drier, medicinal, (iii) *European*, produced in Belgium, Greece and Yugoslavia, of better quality than the above. (iv) *Persian*, harder and contains natural gum.

It has many alkaloids, combined with meconic, lactic or sulphuric acid and some are free. Important among them are *morphine* ($C_{17}H_{19}NO_3$), about 10% : *codeine* ($C_{18}H_{21}NO_3$), 0.5% : *narcotine* ($C_{21}H_{23}NO_7$), 6% : *narceine* 0.2% : *papaverine* ($C_{20}H_{21}NO_4$), 1% and *thebaine* ($C_{19}H_{21}NO_2$), 0.3%. Of these morphine is present in largest proportion and more important.

Certain indifferent substances as mucilage, resin, glucose, fat, caoutchouc, essential oils and salts of ammonium, calcium and magnesium are also present.

OFFICIAL PREPARATIONS.—(i) *Opium Pulveratum* (*Opium Pulverat.*), Powdered opium ; opium is dried at a moderate temperature, made into fine or moderately fine powder and *standardised* to contain 10% of anhydrous morphine. In 3 gr., 3/10 gr. of morphine. Dose, ½ to 3 grains or 30 to 200 mg. (ii) *Pulvis Cretæ Aromaticus cum Opio* (*Pulv. Cret. Aromat. c. Opio*), See p. 53. Morphine, 0.25%. Dose, 10 to 60 grains or 0.6 to 4 grammes. (iii) *Pulvis Ipecacuanhæ et Opii* (*Pulv. Ipecac. et Opii*), *Dover's powder*, See p. 53. Containing 10% of opium and 1% of morphine. 10 gr. (0.6 g.) has 1/10 gr. (6 mg.) of anhydrous morphine. Dose, 5 to 10 grains or 0.3 to 0.6 gramme. (iv) *Tabellæ Ipecacuanhæ et Opii* (*Tab. Ipecac. et Opii*), See p. 57. Dose as of powder of Ipecacuanha and Opium. If the quantity is not stated, 5 gr. tablets are supplied. (v) *Tabellæ Acidi Acetylsalicylic cum Ipecacuanha et Opio* (*Tab. Acid. Acetylsalicyl. c. Ipecac. et Opio*). See p. 56. Dose one to 2 tablets : each tablet contains 2½ gr. of each of Acetyl Salicylic Acid and Powder of Ipecac. and Opium. (vi) *Tinctura Opii* (*Tinct. Opii*), *Laudanum*. See p. 59. *Standardised* to contain 1% w/v of dry morphine : in 30 min. ½ gr. of morphine. Dose, 5 to 30 minims or 0.3 to 2 ml. (vii) *Tinctura Opii Camphorata* (*Tinct. Opii Camp.*), *Paregoric*, *Paregoric Elixir*. See p. 59. Contains 1/30 gr. of morphine in 60 min. or 0.05%. Dose, 30 to 60 minims or 2 to 4 ml.

UNGUENTUM GALLÆ CUM OPIO (Not official).—Powdered opium 7.5, gall ointment 92.5 (containing 1 in 13½ or 7½% of opium).

INCOMPATIBLES.—Solution of ferric chloride gives a red colour due to meconic acid. Salts of zinc, copper, arsenic, silver nitrate and lead acetate or subacetate precipitate alkaloids : all alkalies precipitate morphine and narcotine. See p. 88. Oxidising agents destroy morphine.

1. MORPHINÆ HYDROCHLORIDUM (*Morph. Hydrochlor.*), $C_{17}H_{19}O_3N, HCl, 3H_2O$.

It is the hydrochloride of the alkaloid, morphine obtained from opium. It occurs in silky prisms or white acicular or minute cubical crystals or crystalline powder. It contains 74.2 to 76.2% of the anhydrous alkaloid. Soluble in 25 of water, 50 of alcohol (90%) and in 8 of glycerin : insoluble in solvent ether and chloroform. Morphine was first isolated by Serturmer in 1804.

Dose, ½ to ⅓ grain or 8 to 20 mg.

OFFICIAL PREPARATIONS.—(i) *Liquor Morphinæ Hydrochloridi* (*Liq. Morph. Hydrochlor.*), See p. 50. Strength, 1% of morphine hydrochloride).

Dose, 5 to 30 minims or 0.3 to 2 ml. (ii) *Suppositorium Morphinæ* (*Supp. Morph.*), See p. 55. $\frac{1}{2}$ gr. of morphine in each. (iii) *Trochiscus Morphinæ et Ipecacuanhæ* (*Troch. Morph. et Ipecac.*), See p. 61.

TINCTURA CHLOROFORMI ET MORPHINÆ COMPOSITA (Not official).—Contains $\frac{2}{3}$ min. of chloroform, $\frac{1}{2}$ min. of diluted hydrocyanic acid and 1/11 gr. of morphine hydrochloride in 10 min.

Dose, 5 to 15 minims or 0.3 to 1 ml.

2. MORPHINÆ SULPHAS (*Morph. Sulph.*), Morphine Sulphate, $(C_{17}H_{19}O_3N)_2, H_2SO_4, 5H_2O$.

Morphine sulphate is the sulphate of the alkaloid morphine, obtained from opium. White acicular crystals, cubical masses or white crystalline powder, inodorous with a bitter taste, soluble in 24 of water, 700 of alcohol (95%) and insoluble in ether and chloroform. This contains 73.5 to 75.5% of anhydrous morphine.

Dose, $\frac{1}{4}$ to $\frac{1}{2}$ grain or 8 to 20 mg.

(i) *Injectio Morphinæ Sulphatis* (*Inj. Morph. Sulph.*), See p. 44. Dose as of Morphine sulphate.

(ii) *Injectio Morphinæ et Atropinæ* (*Inj. Morph. et Atrop.*), See p. 44. Dose, 8 to 15 minims or 0.5 to 1 ml. subcutaneously.

MORPHINÆ TARTRAS (*Morph. Tart.*), Morphine Tartrate. (Not official).

A white powder or minute acicular crystals, soluble 1 in 11 of water and sparingly in alcohol (90%), chloroform or ether.

Dose, $\frac{1}{8}$ to $\frac{1}{2}$ grain or 0.008 to 0.02 gramme.

3. PAPAVERINÆ HYDROCHLORIDUM (*Papaver. Hydrochlor.*), $C_{20}H_{21}O_4N, HCl$.

Papaverine hydrochloride is the hydrochloride of alkaloid *papaverine* obtained from opium or by synthesis. White inodorous, slightly bitter crystals or crystalline powder : soluble in about 40 parts of water, soluble in alcohol (90%), in chloroform but not in anæsthetic ether.

Dose, 2 to 4 grains or 0.12 to 0.25 gramme.

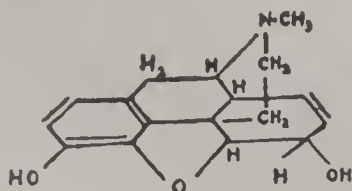
INCOMPATIBLES.—All alkaloidal precipitants including alkalies, soluble salts of heavy metals and all vegetable preparations containing tannin.

SYNTHETIC PREPARATIONS.—Morphine has not been synthetised : but from this several have been made. Although codeine is naturally present in opium, about half of total available morphine is made into it. Thus *codeine* is methyl morphine, *dionine* is ethyl morphine. *Heroine* is morphine ester. *Dilaudid*, *dicodide* and *Eucondal* are oxidation products of morphine. *Apomorphine* is morphine minus one molecule of water.

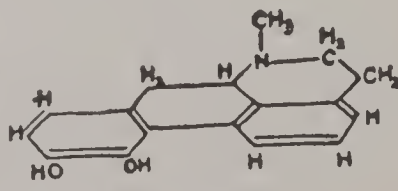
Pharmacology [and Therapeutics]

The alkaloids of opium are divided into two groups :

(i) PHENANTHRENE-PYRIDINE GROUP, containing morphine, codeine and thebaine.



Morphine



Apomorphine

Some alkaloids are prepared artificially from morphine : apomorphine, dionine, heroine, eucondal, dicodide, dilaudid and peronine.

(ii) BENZYL-ISOQUINOLINE GROUP, containing papaverine, laudanosine, laudanine, narcotine and narceine.

Also hydrastine, hydrastinine (from laudanosine) and cotarnine (from narcotine); these have allied structural formulæ.

The action of both these groups on the central nervous system is almost the same, namely, progressive selective depression of different centres of the brain especially of the cerebral, sensory and the respiratory centres. But the first group increases the tone of the plain muscles and the second, causes their relaxation.

As opium contains more morphine than any other alkaloids, its pharmacological action is mainly of morphine.

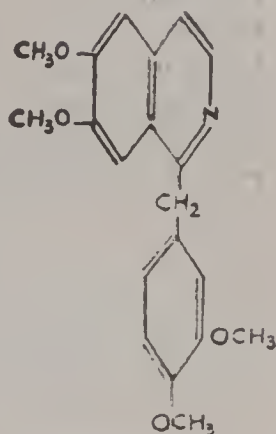
Structurally, morphine has two OH (one phenolic and the other, alcoholic). In codeine, phenolic OH is replaced by methyl radicle: in dilaudid, alcoholic OH is replaced by a ketone group and adjacent double bond is hydrogenated.

The essential analgesic and narcotic actions of morphine rest chiefly in phenolic OH: when this is removed, analgesia is lessened as in codeine.

APPLIED EXTERNALLY, on the intact skin, opium has practically no action as it is not absorbed, but applied to the raw surface, it is partly absorbed and produces its specific action. In such cases, there may be slight local analgesia relieving pain but this is hardly very much.

TAKEN BY THE MOUTH, a part of it is absorbed from the stomach, and the rest, from the small intestine. Its main action is one of depression of the central nervous system with special selective affinity for the pain sense and the respiratory centres. The actions may be classed under three heads; those on the cerebral hemispheres, the medulla and on the spinal cord.

(i) CEREBRUM.—Given in small doses as 7.5 mg. or $\frac{1}{8}$ grain of morphine, some persons experience a short period of excitement: there is an exuberance of imagination, diminished power of reasoning and judgment so that the mind wanders from one subject to another, ideas flow rapidly with a certain degree of exhilaration. Although the higher cerebral functions are often maintained quite normal, these are not appreciably stimulated at any period: the lower ones may get a period of uncontrolled activity. The successive events also in the same way, follow the "law of dissolution". The result is a stage of pleasant drowsiness. This is associated with heaviness of the limbs, dulling of perception especially of pain sense and a desire to be left alone. This condition, known as "euphoria", leads to opium addiction.



Papaverine

But the most important action of opium is its power of depressing the centre for perception of **pain**. This is the most constant effect. An excruciating pain is relieved even by a moderate dose of $\frac{1}{6}$ th or $\frac{1}{4}$ th grain, a dose not sufficient to cause depression of other cerebral functions or even sleepiness. [Opium is often prescribed as an **analgesic**, best given as a preparation of morphine hypodermically, in $\frac{1}{6}$ th to $\frac{1}{2}$ grain dose and this is its most important therapeutic use.

Although a *constant pain* is relieved, a sudden stimulus causes as much pain as without morphine. Probably morphine *lessens the power of attention* and an individual under it, remains almost unconscious of a constant stimulus but can be roused by a sudden intense stimulus: he, however, relapses to his former lethargy after some time and loses the sense of pain (Cushny). The *pain threshold* is also probably raised which interferes with pain perception (Wolff).

This stage, if the dose is big enough, as 15 mg. or $\frac{1}{4}$ th grain or more of morphine, is succeeded by deep sleep, resembling natural sleep often with no after-effect. But some people feel sick, languid and have persistent headache especially if the kidneys are diseased. Opium is a powerful **hypnotic** and it is specially indicated in *insomnia due to pain*. In other cases of insomnia, barbiturates are more often prescribed.

[A preliminary hypodermic injection of morphine is often a helpful pre-anæsthetic **basal narcotic**: the patient quietly goes under without a stage of excitement and struggle. Morphine along with scopolamine is helpful for inducing "twilight sleep", to be described afterwards].

Other **sensations** as of light, sound or tactile discrimination and various **mental functions** are not as markedly depressed.

Reflexes tends to become somewhat sluggish. The tendency to cough becomes lessened. This is mainly from depression of the respiratory centre. [Opium preparations such as morphine or codeine are frequently given for relieving irritable cough with no expectoration].

The **motor cells** of the brain are not **affected** by a small dose; the excitability to electrical stimuli of the cerebral motor area in an experimental animal remains normal. (This is a point of difference between opium and the narcotics of the methane series as alcohol or chloroform which affect all nerve cells, motor and sensory). So the anticonvulsant action of morphine is not of a high order. But bigger doses diminish the excitability.

In rare cases, the stage of excitement may be unduly prolonged and the patient becomes almost maniacal. Such a condition is more common in women and children with a highly emotional temperament.

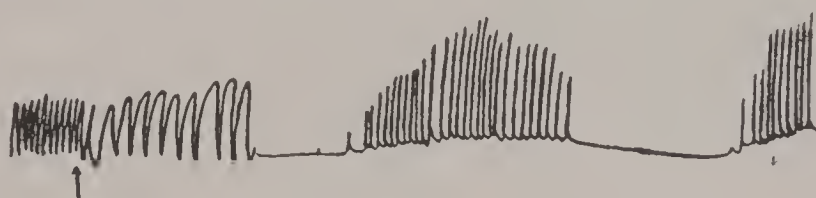
Pupils are greatly **contracted**: often no bigger than a pin's head, due to the stimulation of the oculomotor centres in the floor of the aqueduct of Sylvius.

The stimulation is probably of the *upper centre* in the cortex as in a dog myosis disappears on removal of the cortex (Amsler).

In addition, probably the sympathetic nerve centre in the hypothalamus supplying the radiating fibres of the iris is depressed. As neostigmine increases the constriction, the action is likely to be *cholinergic*.

(ii) **MEDULLA.**—Even in small doses, morphine depresses the **respiratory centre** in the medulla although cardiac inhibitory (vagal), vomiting, salivation and sweating centres are stimulated. This is the other *specialised action*. The respiration becomes slower, and rather shallower. If sleep follows, less CO_2 is formed in the tissues and in spite of slow breathing it does not accumulate in the blood. But if the slowing is great and CO_2 is not sufficiently eliminated, the respiratory centre is stimulated and the breathing becomes deeper than usual but the rate does not very much increase.

If given in large doses, as 1 to 2 grains, the respiratory centre is profoundly depressed; the respiratory movements are markedly diminished in frequency, may be 6 to 8 per minute and become very feeble, irregular and shallow. Before death, these often assume Cheyne-Stoke character. The blood in



(After Cushny)

Fig. 28.—The effect of morphine on respiration. This is made immediately slow and shallow: afterwards deeper (effect of asphyxia) and finally Cheyne-Stocky.

consequence is less oxygenated and the patient becomes **cyanotic**. Notwithstanding this condition of asphyxia, the pupils remain contracted till death is neared when these are dilated. This is an unusual combination because in all other cases of asphyxia, the pupil is dilated. This is therefore a valuable guide in the diagnosis of opium poisoning.

Morphine relieves cardiac dyspnoea by depressing the central sensory mechanism and is useful in cardiac asthma.

(iii) **MOTOR CELLS OF THE SPINAL CORD.**—At first opium causes **slight depression** which may be followed by **hyperexcitability**, as twitchings and tremors or even tetanic convulsions in the terminal stage. This is due to the increased receptivity of the posterior roots of the spinal cord and is more marked in lower animals especially in frog with poor development of the cerebrum; more common with laudanine and thebaine and the least with morphine.

In a human being, quicker respiratory failure brings in the fatal termination and the stage of hyperexcitability, as is seen in cold blooded animals, does not find time to appear.

(iv) **PERIPHERAL NERVES** are unaffected ; local application of an opium preparation does not cause any analgesia. Skin sensibility may be slightly lowered by a subcutaneous injection but this is almost wholly from the central action.

To sum up, opium causes selective depression of the *respiratory* and *pain sensation centres* with a dose that does not appreciably affect other centres and with a big dose, death follows from respiratory failure. Further, the cerebrospinal axis is also *depressed* from above downwards and somewhat *stimulated* from below upwards.

CIRCULATION.—With a moderate, therapeutic dose, there is **no decided action** of morphine, either on the cardiac centre or on the cardiac muscles. The heart rate may be temporarily slightly increased if vomiting is present. The blood pressure is unaltered and the arteries are of normal size but, due to slight depression of the vasomotor centre, or from some undetermined cause, the blood vessels of the skin are dilated : this is accompanied by a feeling of warmth and sometimes considerable itching. Opium thus acts as a mild **diaphoretic** and slightly **antipyretic**. See p. 512.

If asphyxia is marked, the heart rate is usually slowed and the blood pressure varies : it may be raised on account of asphyxia or lowered from slow heart rate.

Morphine dilates the **coronary arteries** and relieves dyspnoea of heart disease : used in coronary thrombosis and cardiac asthma.

BLOOD CHANGES.—The addicts may have blood hydration which tends to disappear on withdrawal of morphine. A single therapeutic dose may not cause any constant change of the red blood corpuscles but the sedimentation rate is often increased and leucocytosis may be caused.

ALIMENTARY CANAL.—Morphine lessens appetite and causes constipation. Colic, if present, is relieved. It may cause nausea.

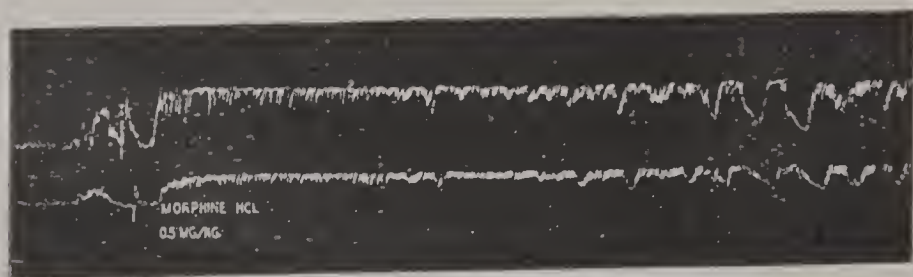


Fig. 29.—Morphine effect on the intestine. Tracings taken by putting two balloons in lower ileum of a dog. Shows tonic contraction of the intestine after 0.5 mg. of morphine per kg. body weight.

and vomiting more marked when the sedative effects of the drug is nearly disappearing. But these actions of morphine have not been quite fully explained in some of its items. It has **central** (especially in the medulla) and **peripheral actions**.

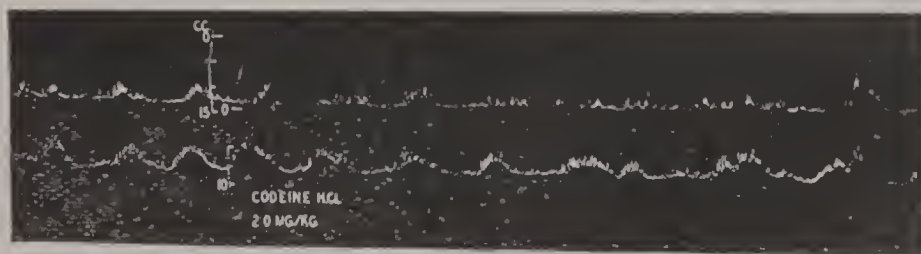
(a) The *medullary action* causes occasional nausea and vomiting especially after hypodermic injection, more marked in some persons than in others. This is often a personal idiosyncrasy and sometimes more marked in persons with renal insufficiency. This may be apparent several hours after its administration and more marked in lower animals as in dogs.

(b) The *peripheral action* as has been observed in unanæsthetised dogs, causes contraction, first of the cardiac and then of the pyloric sphincters but decrease of tone of the central portion and relaxation of the gastric muscles. The force and frequency of gastric peristalsis are lessened: the food is retained longer and it enters the duodenum rather slowly. The small intestine shows increased muscular tone and decrease of the peristaltic waves. The large intestine also shows increased muscular tone but to a lesser degree and lessened forward movement of the contents. The sense of hunger is also lessened: central sedation is probably the main reason.

As an effect of entry of the gastric contents in a small quantity at a time, with increased intestinal tone and diminished propulsive action also diminished glandular secretions, the contents are retained longer favouring absorption of the fluid and making these drier. At the same time the defæcation reflex is made sluggish and the anal sphincter is more contracted. All these cause **marked constipation**. The effects produced in the human being are also identical. (Cushny).

The nature of the action is not quite clear. It has been found that morphine effect is increased by neostigmine and diminished by atropine. So the action may be *cholinergic*.

Codeine has similar action but feebler. *Diamorphine* causes less nausea and vomiting but its constipating action is 1.5



(Krueger from Cushny)
Fig. 30 — Codeine effect on the intestine, Tracings taken in the same with 2 mg. codeine per kg. body weight.
Codeine does not cause any contraction.

times greater than that of morphine. *Papaverine* has weak gastric and even more so intestinal effects: under experimental condition, it tends to lessen the peristalsis of the colon and relax the isolated portions of unstriated muscle fibres. Some synthetic preparations resembling it (as EUPACO) are used as **antispasmodic**.

[Next to its action on the nervous system for the relief of pain, opium preparations are used for this **constipating** effect, for controlling diarrhoea and chronic dysentery. In fact, it is useful in all conditions requiring a limitation of intestinal movement].

This constipating effect is better manifested by opium itself than by morphine as the former contains the alkaloids of the isoquinoline group also (narcotine and papaverine). Further owing to its less absorbability, opium remains longer in contact with the mucous membrane of the alimentary canal to produce its local effect there than morphine.

OTHER UNSTRIPED MUSCLES.—In animals, the morphine group (phenanthrene) causes increased **contraction** and **tonicity** of the muscles of the biliary tract, ureter and the urinary bladder and to a less extent, of the bronchi and uterus. These are thought to be due to peripheral cholinergic action. But the isoquinoline group as papaverine depresses them causing relaxation.

Yet morphine relieves the pain of biliary and renal colic by its powerful central analgesic action.

Morphine sometimes causes **retention of urine** due to contraction of the sphincter of the outlet.

GLANDULAR SECRETIONS.—The **secretion** of most of the **glands diminishes**. This applies specially to those of the intestine and bronchus, also to a less extent of the secretions of milk and urine. Salivation may be increased at first but afterwards, it is so greatly decreased that even with a moderate dose, there is marked dryness of the mouth and throat. But it causes profuse secretion of sweat, especially in a moderately big dose. [Compound powder of Ipecacuanha and opium is often given in 10 grs. dose usually with acetyl salicylic acid 5 grs. at bed time in the beginning of coryza to act as **diaphoretic**].

The **gastric**, the **biliary** and **pancreatic secretions** are lessened. Their deficiencies impair digestion.

METABOLISM.—The general metabolism is slightly **lowered** especially if given in large doses. This is more marked with the first few doses. The excretion of nitrogenous products and CO_2 and the intake of O_2 are lessened. In diabetes mellitus, the amount of sugar in the urine diminishes; this is probably due to the delay in the absorption of carbohydrate. In some cases, blood sugar rises with glycosuria: probably due to release of sympathin and complete sympathectomy stops this effect.

Depression of respiration tends to increase lactic acid in the blood and disappearance of glycogen from the liver causing acidosis.

TEMPERATURE is **slightly lowered**, partly from diminished muscular activity but mainly from **vasodilatation** and **diaphoresis** causing increased radiation. The heat producing centre

is depressed, so that external heat or cold causes greater effect on the body temperature. [A person with opium poisoning should not be exposed to chill].

EXCRETION.—Recent observations showed that bulk of the morphine is excreted by the **kidneys** and a small fraction in the fæces : minute quantities have been found in the saliva, milk and sweat. The total urinary excretion is about 80 to 92% in a nontolerant animal and 45% in a tolerant animal. Of this only 10% is “free” morphine (previous observers took cognisance of this amount only) and 90%, “combined” morphine. The amount of free morphine excreted is the same in both tolerant and nontolerant animals and in the former, less of combined morphine is excreted. What happens to this loss is not quite clear, may be destroyed in the system being conjugated in the liver. (Thompson and Gross, 1941). Oberst (1941) found that in the human being “free” and “combined” amounts were about half of what recovered from the dogs : in the addicts, the proportion is 5 and 30%. By increasing the dose of morphine, more of “combined” fraction is excreted. Gross (1942) thinks that “combined” form is responsible for analgesia and its increased excretion indicates that the tissues retain the necessary amount and excrete the surplus. Slaughter (1943) found that neostigmine decreases the excretion of both types and potentiates morphine analgesia. Only about 5% is excreted in the fæces, all in “free” form.

IDIOSYNCRASY AND TOLERANCE.—Few drugs show more personal peculiarities than opium. Thus, some show more preliminary excitement and vomiting ; the others are more easily narcotised even with a comparatively small dose or complains of dryness of the mouth. Women are more easily affected than men and children are specially susceptible.

Patients suffering from advanced kidney, liver and lung diseases badly stand opium preparations ; so great care should be taken in prescribing these to such patients.

The addicts develop considerable tolerance. Whereas 0·3 gm. of morphine is the usual fatal dose, a morphinomaniac is known to stand as much as 5 gm. a day. The mechanism of tolerance is unknown : one such may be formation of a larger percentage of combined morphine in the system.

To sum up the Actions—

(1) **EXTERNALLY**, opium has no definite action except probably of being **slightly analgesic**^{340, 342}, especially on the mucous membranes of contact.

(340) R

Cataplasma Opii

Linseed Poultice is prepared and tincture of opium is sprinkled on it. For superficial inflammation.

(341) R

Opium gr. 1

Acid. Tann. gr. 5

Ext. Bellad. Sicc. gr. ½

Ol. Theobrom. gr. 15

Suppository for painful piles.

(St. Bart's.)

(2) **INTERNALLY**, it is a valuable remedy for the relief of **pain** especially of various types of **colic**. The action is pronounced and prompt and not equalled by any other analgesic. Morphine³⁴³⁻³⁴⁴ is more frequently chosen than either the "whole" opium or its any other alkaloid and is best given hypodermically.

Hypodermically, morphine is a valuable **hypnotic**, being very dependable where sleeplessness is due to pain and other hypnotics fail. Unless the liver and the kidneys are much diseased or the lungs œdematous, it may be given with benefit in nocturnal distress of heart disease also.

Personal idiosyncrasy may cause troublesome vomiting, cerebral excitement or deep coma even with a comparatively small dose.

(3) To lessen **diarrhœa** by limiting the movements of the intestine³⁴⁵⁻³⁴⁷, it is invaluable. For that purpose, tincture of opium is the best. It is also valuable in **internal hæmorrhage**, morphine hydrochloride gr. $\frac{1}{6}$ to $\frac{1}{4}$ hypodermically is preferred.

(4) To relieve **cough**³⁴⁸⁻³⁵⁰, it is often chosen. Various opium preparations, as camphorated tincture of opium, heroine hydrochloride and codeine are made into linctus with syrups for the relief of irritating cough especially that of pulmonary tuberculosis.

(5) As a mild **diaphoretic**, Dover's powder is sometimes given in ordinary cold or for a attack of influenza.

(342) B
Tinct. Opii min. 20
Mucil. Amyl. fl. oz. 2
Per rectum in acute dysentery
with tenesmus

(343) B
Morph. Hydrochlor.
gr. $\frac{1}{4}$ to $\frac{1}{2}$
Atrop. Sulph. gr. $\frac{1}{60}$
Aq. Steril. min. 15
For hypodermic injection.

(344) B
Liq. Morph. Hydrochlor.
min. 10
Phenazon. gr. 10
Aq. Camph. ad. fl. oz. 1
For dysmenorrhœa.

(345) B
Tinct. Opii min. 10
Acid. Sulph. Dil. min. 15
Tinct. Cardam. Co. min. 30
Aq. Cinnam. ad. fl. oz. 1
For acute diarrhœa.

(346) B
Liq. Morph. Hydrochlor.
min. 15
Bism. Carb. gr. 10
Tinct. Cardam. Co. min. 30

Aq. Chlorof. ad. fl. oz. 1
For painful dyspepsia.

(347) B
Glycer. Pepsin. min. 60
Tinct. Opii Camph. min. 20
Aq. Cinnam. ad. fl. oz. 1
A helpful digestive.

(348) B
Tinct. Opii Camph. min. 120
Syr. Prun. Serot. min. 90
Oxymel. Scill. min. 60
Chlorof. min. 5
Tinct. Seneg. ad. fl. oz. 1
One tea-spoonful for chronic
bronchitis.

(349) B
Liq. Morph. Hydrochlor. min. 4
Sp. Chlorof. min. 10
Syr. Tolu. min. 30
Syr. Prun. Serot. ad. min. 60
(Lucas)

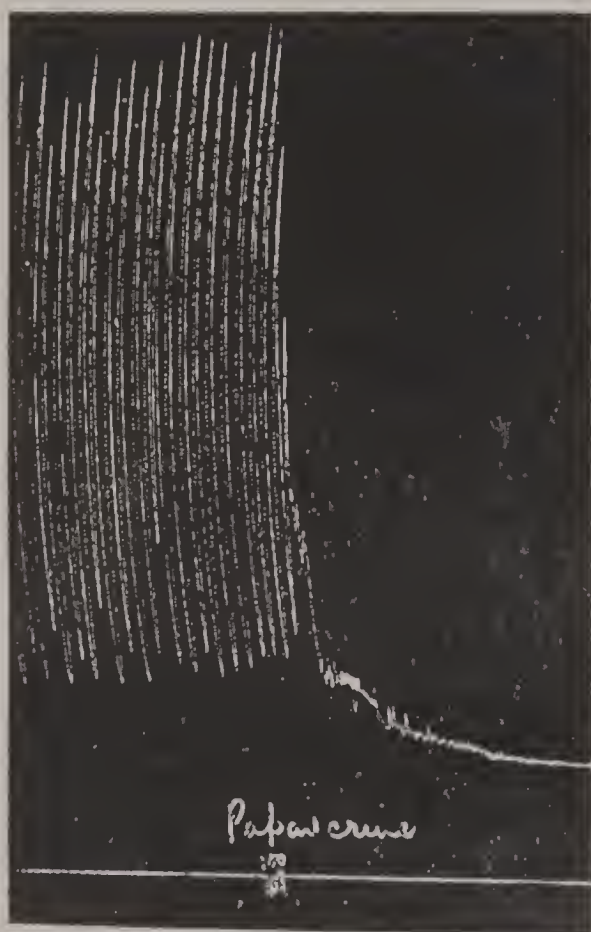
Linctus for troublesome cough.
(350) B
Pot. Acet. gr. 15
Tinct. Opii Camph. min. 20
Syr. Tolu. min. 60
Aq. Chlorof. ad. fl. oz. 1
For acute bronchitis.

(6) Care should be taken not to give it too frequently, especially for chronic and relapsing pain for fear of **forming a habit** and not more than a very minute dose should be given to infants: a new born is proportionately ten times more susceptible].

SUMMARY.—*Opium* is used for controlling diarrhoea and morphine for relieving pain, sometimes used as cough sedative. Susceptibility of children and chance of respiratory depression and of habit formation are to be kept in mind.

Papaverine

Papaverine is the most important alkaloid of benzyl-isoquinoline group and used as hydrochloride. It is readily absorbed from oral administration and may also be given subcutaneously.



(Dixon)
Fig. 31.—Effect of Papaverine 3 mg. in 100 ml. of Ringer solution. Marked relaxation of the intestinal movements.

NERVOUS SYSTEM.—The intensity of narcotic action is intermediate between morphine and codeine. It has very little action on the central nervous system and in a therapeutic

dose, it is neither hypnotic nor analgesic. It has however slight **local anæsthetic** action. In bigger doses, it increases the reflex excitability and in very big doses causes tetanic spasm of spinal origin (as distinguished from codeine which excites the brain stem).

UNSTRIPED MUSCLES.—The most important action is on the smooth muscles relaxing them especially if these are in spasm. The tone is lessened and amplitude and frequency of contraction are decreased. The action is best seen in the musculature of the *blood vessels*.

CARDIOVASCULAR SYSTEM.—The heart is slowed by direct action on the muscles. The blood vessels are relaxed and the blood pressure is lowered.

Papaverine has been found useful in peripheral or pulmonary arterial embolism. Given intravenously in 20 to 100 mg. (usually 50 mg.) doses, it increases the collateral circulation and by improving the blood supply, relieves pain and restores function of the affected area. It is also useful in coronary infarction, peripheral vascular disease threatening gangrene and in Raynaud's disease. It is of some value in pruritus (orally 1 to 1½ gr. 3 to 4 times daily).

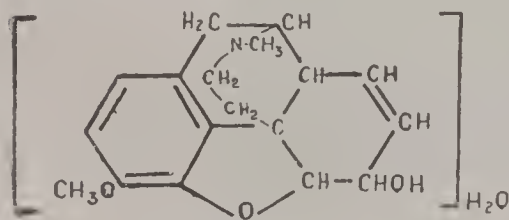
Papaverine moderately relaxes the *bronchi*, *gastro-intestinal tract*, *bile-passages* and the *ureters* also. This is more marked in the excised portions. But therapeutically it is not so useful in spasmodic conditions in places other than the blood vessels. It has **some quinidine action** on the heart muscles raising the fibrillation threshold but not used for this purpose.

Papaverine does not appear in the urine and probably it is wholly destroyed in the tissues. There is no habit formation.

SUMMARY.—The main action is as **spasmolytic** especially on the *blood vessels*. It is a mild *local anæsthetic* and moderately *narcotic*.

OTHER ALKALOIDS OF OPIUM OR PREPARED FROM OPIUM

1. **CODEINA** (*Codein.*), Codeine, $C_{18}H_{21}O_3N$, H_2O , Morphine methyl ether.



Colourless or translucent trimetric crystals or crystalline powder, inodorous and bitter, obtained from opium or by methylation of morphine. It is soluble at 15.5° in 120 parts of cold water, in 2 of alcohol (90%), in 75 of solvent ether: freely in chloroform. An aqueous solution is alkaline to

litmus. This was first isolated by Robiquet (1832).

DOSE, ⅙ to 1 grain or 10 to 60 mg.

2. **CODEINÆ PHOSPHAS** (*Codein. Phosph.*), Codeine Phosphate, $C_{18}H_{21}O_3N$, $H_3PO_4H_2O$.

This is the phosphate of the alkaloid codeina: contains 69.5% of codeine, $C_{18}H_{21}O_3N$.

Granular, inodorous, snow-white acicular crystals or crystalline powder, soluble in 4 of water (the solution is acid to litmus) and in 250 of alcohol 90%.

Dose, $\frac{1}{6}$ to 1 grain or 10 to 60 mg.

Codeine and its salts should be kept in a well-closed container away from light.

OFFICIAL PREPARATIONS.—(i) *Tabellæ Codeinæ Phosphatis* (*Tab. Codein. Phosph.*), See p. 56. Strength is between 87.5 to 110.5% of codeine phosphate. Dose, same as of codeine phosphate. Each tablet, if not otherwise stated should contain $\frac{1}{2}$ grain. (ii) *Tabellæ Codeinæ Compositæ* (*Tab. Codein. Co.*), See p. 57. Dose, 1 to 2 tablets. Each tablet contains acetylsalicylic acid and phenacetin each 4 gr. (0.2592 g.) and codeine phosphate $\frac{1}{8}$ gr. (8.1 mg.).

SYRUPUS CODEINÆ PHOSPHATIS (Not official).—Codeine phosphate 5, distilled water 15, syrup to make 1000, containing 0.27 gr. of codeine in 60 minims.

Dose, 30 to 120 minims or 2 to 8 ml.

3. APOMORPHINÆ HYDROCHLORIDUM (*Apomorph. Hydrochlor.*), Apomorphine Hydrochloride, $C_{17}H_{17}O_2N, HCl, \frac{1}{2}H_2O$.

This is obtained from morphine by subtraction of one molecule of water by heating it with an excess of hydrochloric acid in sealed tubes. Small, colourless or greyish white glistening crystals taking a greenish tint on exposure to air and light. It is soluble at 15.5°, in 50 of water and in alcohol (90%). Less soluble in solvent ether.

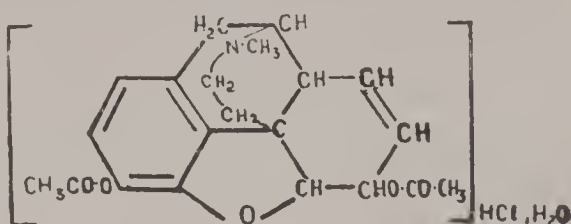
Dose, $\frac{1}{32}$ to $\frac{1}{8}$ grain or 2 to 8 mg., emetic subcutaneously.

Injectio Apomorphinæ Hydrochloridi (*Inj. Apomorph. Hydrochlor.*): See p. 42.

If the strength is not stated, a solution with 1.20 gr. in 15 minims or 3 mg. in 1 ml. is dispensed.

4. DIAMORPHINÆ HYDROCHLORIDUM, (*Diamorph. Hydrochlor.*), Heroin Hydrochloride, $C_{21}H_{23}O_5N, HCl, H_2O$.

Diamorphine is *diacetylmorphine* and is obtained by the action of acetic anhydride on morphine. A colourless and odourless crystalline powder with a bitter taste. Soluble in 2 parts of water and in 11 of alcohol (90%). Insoluble in solvent ether.



Dose, $\frac{1}{12}$ to $\frac{1}{6}$ grain or 5 to 10 mg.

Pharmacology [and Therapeutics]

Codeine

NERVOUS SYSTEM.—Codeine acts on the central nervous system much less powerfully than morphine. To induce sleep or to relieve pain, at least 4 times the dose of morphine is necessary. Yet sleep is not as refreshing and deep. A bigger dose, for inducing deeper sleep, causes excitement, restlessness and exaggerated reflexes. So it is of no value either as analgesic or as hypnotic. Given with coal tar analgesics as aspirin and phenacetin, it tends to intensify their effect by synergism and such combination is often prescribed orally.

The signs of excitation are more common in lower animals especially manifested in the spinal cord shown by increased reflexes and muscular spasms.

RESPIRATORY CENTRE is moderately depressed : the rate is slightly slowed and the **cough reflex lessened**. It does not lessen the bronchial secretions. [Codeine is used frequently to make cough-linctus³⁵¹⁻³⁵²]. Codeine phosphate being more soluble, is often prescribed.

Pupils are only moderately contracted but if the reflex excitability is increased, these are dilated.

The depressant action on the *sympathetic nerves* is greater than that of morphine causing greater **vaso-dilatation** and **fall of blood pressure**.

Its action on the plain muscles is less than that of apomorphine, but more than of morphine. Consequently, a hypodermic injection of the drug may sometimes cause **vomiting** and very rarely **purging**.

A narcotic dose given orally causes **constipation** but less than that of morphine. Unlike morphine, tolerance is not established because the drug is not oxidised in the system. Sometimes symptoms of intolerance appear as nausea and vomiting even with a moderate dose.

It causes *less euphoria* and has **less tendency to form habit** and during the breaking off of morphine addiction, codeine is thought to be a less dangerous substitute but not quite safe as 5 times the dose of morphine is necessary to cause the same effect. It sometimes **reduces glycosuria** in diabetes mellitus³⁵³ and was formerly given for this condition.

It is *excreted* by the kidneys unchanged.

SUMMARY.—Codeine causes less *analgesia*, *euphoria* and *hypnosis* also less depression of the *respiratory centre* than morphine : used as **cough sedative** and **analgesic** along with coal-tar analgesics.

APOCODEINE (Not official) has nicotine-like action paralysing the sympathetic ganglia and is of no therapeutic value.

Apomorphine Hydrochloride

Apomorphine is produced by dehydrating morphine, losing one molecule of water. Its main actions are like morphine, on the central nervous system and on the **vomiting centre** in the medulla but, unlike morphine, the cerebrum is only slightly

- (351) R
Syr. Codein. Phosph.
Syr. Prun. Serot.
Oxymel Scill.
Syr. Tolu. aa. min. 120
One tea-spoonful for irritating
cough.
(352) R
Codein. gr. $\frac{1}{4}$
Bromoform min. 1
Alcohol (90%) min. 20

- Syr. Tolu ad. fl. oz. 1
One tea-spoonful for whooping
cough.
(353) R
Codein. gr. $\frac{1}{4}$
Ext. Nuc. Vom. Sicc.
Ext. Bellad. Sicc. aa. gr. $\frac{1}{4}$
Ext. Case. Sagr. Sicc. gr. 1
Glycer. Trag. q.s.
Pil. One 2 to 3 times daily for
diabetes mellitus.

depressed whereas the vomiting centre is powerfully excited causing vomiting in 5 to 10 mg. dose in 5 to 15 minutes and for this action, this is the most powerful of all drugs in the morphine group.

Given hypodermically, it acts with great certainty, as a rule, within 5 minutes and is seldom delayed beyond 12 minutes. After vomiting, the feeling of nausea quickly passes off without any after-effect although in a few cases marked depression, weakness and even collapse may follow. As this in solution applied locally to the medulla causes vomiting, the action is central medullary and not locally gastric. [It is more advantageous than an oral emetic, as it can be given by injection to a patient who is unconscious or unwilling to take medicine by the mouth]. The action is rapid and its depressing effect on the pulse and respiration is only temporary. But in a case of poisoning stomach wash is preferred: in narcotic poisoning, it may fail to act. In some cases, profound depression and even coma may follow.

In doses not sufficient to cause emesis as 1 mg., it increases the secretion of the bronchial mucous membrane and is an **expectorant**^{354, 355} aiding the removal of tough mucus [so is helpful in subacute and chronic bronchitis]. Secretions of saliva, tears and perspiration are also increased.

If the solution when shaken with 100 times of distilled water, gives a green colour, it should not be used.

In large doses, it depresses the central nervous system in man. An animal shows signs of excitement as uneasiness and an irresistible desire for movement. In very large doses, it paralyses the central nervous system and death takes place from respiratory failure, the heart still beating.

Recently it has been found that 1 to 2 mg. diluted with normal saline given intravenously it causes **sedation** in delirium, severe excitement and in alcoholic psychosis and may be used as pre-anæsthetic medication. The action is seen in 10 minutes and lasts for about 2 hours. In case of cyanosis, apomorphine should not be used.

SUMMARY.—Apomorphine is an effective hypodermic emetic without causing much depression: a smaller dose intravenously is a cerebral sedative: bigger doses cause respiratory failure.

Diamorphine Hydrochloride

It is more depressant to the cerebral cortex than morphine and is more poisonous also. It acts with a much smaller dose

(354) \mathcal{R}
 Apomorph. Hydrochlor.
gr. 1/80
 Tinct. Ipecac. min. 10
 Syr. Scill. min. 30
 Aq. Chlorof. ad. fl. oz. 1
 An expectorant in chronic bronchitis.

(355) \mathcal{R}
 Apomorph. Hydrochlor. 0.5
 Acid Hydrochlor. Dil. 0.25
 Alcohol (90%), 4.5
 Aq. 4.5
 Syr. ad. 100 (Martindale)
 For chronic bronchitis, 30 to 60 min. for a dose.

and more quickly : it is a more powerful analgesic than morphine being effective in 1.5 mg. (1/40 gr.) dose only. It is a more powerful sedative to the respiratory centre, and so more effectively diminishes the cough reflex. [It is used for relieving irritating cough³⁵⁶]. It was one time more popular than codeine and, like it, is excreted by the kidneys. In a therapeutic dose, it causes less nausea and vomiting but more constipation than morphine and has very little action on the central nervous system. In poisonous doses, it has more marked effect on the cerebrum and medulla and may cause excitement and convulsion. But there are other disadvantages also.

It causes more euphoria and a certain amount of excitement but taken for some time, the tissues get accustomed to it. A progressively larger dose is required forming drug habit. The higher faculties of the brain are enfeebled, the addict becoming a mental and moral wreck. It is thus the most dangerous drug of addiction. Its use has practically been abandoned and its manufacture has been prohibited in America.

SUMMARY.—Diamorphine is more powerful than morphine causing more euphoria (so more habit-forming), analgesia and respiratory depression. It was used as cough sedative but is getting obsolete.

OPIUM POISONING.—*Acute poisoning* is often due to taking a big dose of crude opium for suicidal purpose : rarely a big dose of morphine (as one grain or more) taken subcutaneously.

The effect is increasing sleepiness passing to deep coma with marked slowing of respiration and contraction of the pupil. The smell of opium may be present in the breath.

Treatment is (i) to wash out the stomach with warm water (also weak permanganate solution) and give a mag. sulph. purgative. (ii) If respiration is markedly affected, inhalation of CO₂ in 5 to 10% dilution with oxygen also hypodermic injection of caffeine (and strong tea orally), atropine, leptazol, nikethamide and lobeline.

Chronic poisoning is drug-addiction often commenced from therapeutic administration for chronic bowels or lung diseases and sometimes for pain. It is very difficult to break the habit.

Non-official Preparations

DIONINE, Ethyl Morphine Hydrochloride.—This is an alkaloid, prepared from morphine by heating it with sodium ethylate and ethyl iodide. This has mild morphine action, but is specially used as an *eye lotion* in 1 to 5% solution. Applied to the eye, it causes congestion and swelling of the conjunctiva and exudation of serum. In a few hours, this fluid is absorbed along with it any exudative product of disease in the eye. It is often used in many chronic inflammatory conditions³⁵⁷ of the eye. It is slightly analgesic also. It is sedative to excessive cough reflex and being less habit-forming, is getting popular in *cough linctus* for irritable cough³⁵⁸.

DOSE, Orally as a sedative, $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 16 to 30 mg.

(356) Diamorph. Hydrochlor. gr. $\frac{1}{2}$
Menth. gr. 1
Ol. Abiet. min. 5
Terpin Hydrat. gr. 5
Tinct. Aurant. min. 40
Alcohol (90%) min. 60

Syr. ad. fl. oz. 1
One teaspoonful for a dose.
(357) B
Dionin. gr. 2 to 20
Aq. Dest. fl. oz. 1
Eye lotion, in increasing strength.

DILAUDID, Dihydromorphinone and **DICODINE**, Dihydrocodeinone.—The former is a more powerful analgesic than morphine acting as such with $\frac{1}{4}$ th dose: both these are depressant to the cough centre, less habit-forming than morphine and are not constipating and do not cause much nausea and vomiting. But these are proportionately more toxic also and prescribed in small doses.

Dose, $\frac{1}{24}$ to $\frac{1}{2}$ grain. or 2·5 to 30 mg.

HYCODAN, Dihydrocodeinone bitartrate in 1 to 5 mg. doses is a pleasant cough sedative.

METAPON, methyl dihydromorphine, is useful in severe chronic pain as of malignant disease: available in 3 mg. capsules, may be used 2 or 3 times daily. It is expensive and is not much available.

LIQUOR OPII SEDATIVUS, (Morphine 1·8%). Dose, 5 to 10 minims.

NEPENTHE, Dose, 5 to 15 minims (0·84% of morphine).

OPOIDINE, Dose, $\frac{1}{6}$ gr. tablet, containing total alkaloids of opium for oral use, for opium action.

COTARNINE HYDROCHLORIDE, (Stypticin), prepared from narcotine. In a dose of $\frac{1}{4}$ to $\frac{1}{2}$ grain by mouth or hypodermically, it is given for uterine hæmorrhage. *Styptol*, Knoll, is a hæmostatic for internal use and dysmenorrhœa, used in $\frac{3}{4}$ gr. tablets: may be useful in painful erection and nocturnal enuresis.

CODOPYRIN AND **VEGANIN** tablets contain aspirin 4 grs., phenacetin 4 grs. and codeine phosphate $\frac{1}{6}$ gr. and are analgesic and antipyretic.

GLYCOHEROIN, now called *Glykiron*, contains gr. $\frac{1}{8}$ of codeine phosphate per 60 min. and used for irritating cough in tea-spoonful doses.

PARACODEIN BITARTRATE in $\frac{1}{6}$ gr. doses is a cough sedative.

EUKODAL, Dihydroxy-codeinon hydrochloride is analgesic and sedative and is said to be less toxic than morphine: given in $\frac{1}{8}$ gr. tablets orally or $\frac{1}{6}$ gr. ampoule hypodermically.

OMNOPON, **PANTOPON** are mixtures of all the opium alkaloids: said to cause less nausea and vomiting and have dependable morphine action: available as $\frac{1}{6}$ gr. tablets and $\frac{1}{2}$ gr. ampoules.

NARCOPHIN, morphine narcotine meconate, $\frac{1}{3}$ to $\frac{1}{2}$ gr. dose is used as a hypnotic. Narcotine is less depressant to the respiratory centre.

EUPACO, related to papaverine is said to be more spasmolytic and less toxic. It is given in various types of colic, angina pectoris (coronary dilator), migraine, dysmenorrhœa and in spastic constipation.

Dose, $\frac{1}{2}$ gr. in tablets orally or in ampoules hypodermically.

OTHER CENTRAL ANALGESICS

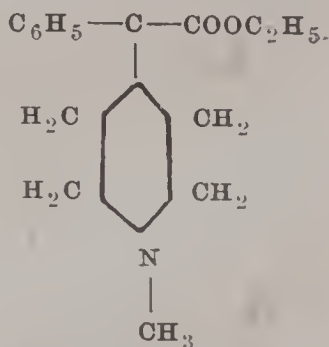
1. **PETHIDINÆ HYDROCHLORIDUM** (*Pethidin. Hydrochlor.*), Dolantine, Demerol and Meperidine, $C_{15}H_{21}O_2N$, HCl.

Pethidine hydrochloride is the hydrochloride of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate, prepared by the interaction of beta-beta'-di (beta-chloroethyl) methylamine and benzyl cyanide, the resulting nitrite being subsequently hydrolysed, esterified and made to hydrochloride: contains not less than 99% of $C_{15}H_{21}O_2N$, HCl.

Dose, $\frac{2}{5}$ to $1\frac{1}{2}$ grains or 25 to 100 mg.

INJECTIO PETHIDINÆ HYDROCHLORIDI (*Inj. Pethidin. Hydrochlor.*) is a sterile solution of Pethidine hydrochloride in water for injection, sterilised by autoclaving or by filtration.

Dose as of Pethidine Hydrochloride. Strength, if not stated, is $\frac{4}{5}$ gr. in 15 min. or 50 mg. in 1 ml. given by subcutaneous injection.



(358) R

Dionin. gr. 1

Acet. Scill. min. 60

Syr. Tolu. ad. fl. oz. 1
One tea-spoonful a dose.

Pharmacology [and Therapeutics]

Pethidine or Isonipecaïne was introduced by Eisteb and Schaumann (1939). Its main pharmacological action has resemblance to (i) *morphine* being analgesic, sedative and euphoric : (ii) to *papaverine* having spasmolytic action on bronchi, intestine and blood vessels and (iii) to *atropine*, having action on the pupil, bronchi and vagus. In addition, (iv) it has a mild local anæsthetic action resembling *cocaine* but being irritating, cannot be used for this purpose.

CENTRAL NERVOUS SYSTEM.—Pethidine is a more powerful analgesic than codeine but less than morphine (ten times bigger dose being necessary) and it does not as effectively relieve sudden acute pain. It is however more effective in relieving pain of *smooth muscle spasm*. *Sedation* and *sleep* is common but may fail in about 15% cases. The pain relieved in about 15 minutes and the effect may last for 3 to 5 hours. In usual therapeutic doses (100 mg.), cough reflex, respiratory and vasomotor centres are not sufficiently affected. *Vomiting* centre is some what depressed in most cases and *euphoria* is quite common.

SMOOTH MUSCLES.—In man, unlike morphine, the smooth muscles of the *bronchi* and the *alimentary canal* from stomach to colon are relaxed : *gall-bladder* and the *ureter* are also relaxed especially if these are in spasmodic state but like morphine, biliary tract is not relaxed. Pethidine is often effective in renal and other types of colic. It has no marked action on the uterine muscles. Unlike morphine it is *not constipating*.

The action is mainly *direct* from action on the muscles and to a less extent on the parasympathetic nerve endings (*anticholinergic*).

CIRCULATION.—Pethidine has no marked action but a large dose, intravenously may cause peripheral vaso-dilatation and lowering of blood pressure. On the heart muscles, it has quinidine action preventing cardiac irregularities and is suitable as pre-anæsthetic medication is cyclopropane anæsthesia. (See p. 474).

The main use is in different **colicky conditions** also in bronchial **asthma**. It is a useful **obstetric analgesic** relieving pain of labour without interfering with uterine contractions : dose is 100 mg. intramuscularly, may be repeated in 4 hours. Pethidine-scopolamine combination (maximum dose of pethidine is 400 mg. and scopolamine 1.3 mg. in 18 hour) is also considered sufficiently safe.

As **pre-anæsthetic medication** it is better than morphine ; it increases the activity of barbiturates and given with due care, minimises the quantity of a general anæsthetic to be used in a surgical operation. It appears to be of special value in cyclopropane anæsthesia in preventing cardiac arrhythmia.

Therapeutically, pethidine is used intramuscularly (subcutaneous injection is irritating and intravenous injection may

cause disagreeable symptoms) in 100 mg. doses. Oral administration is not as effective : absorption takes about 4 hours.

METABOLISM.—Pethidine has no action on the metabolism being readily destroyed by the liver and a small fraction is eliminated by the kidneys. As it is not cumulative the effects soon pass off. It may have to be repeated every 3 to 4 hours.

ADDICTION.—Pethidine may cause *euphoria*, a certain amount of *habituation* and *tolerance* but withdrawal symptoms are less severe than those of morphine. It must be regarded as a drug of addiction. It may partially relieve morphine craving and may be temporarily used during morphine withdrawal.

UNFAVOURABLE SYMPTOMS.—These are sweating and dizziness : occasionally, nausea, vomiting and headache and very rarely nitroid crisis.

Over dose or repeated administration causes toxic symptoms : these are dilatation of the pupils, tachycardia, disorientation and muscular twitchings (like atropine) : occasionally convulsion.

COMMERCIAL PREPARATIONS.—*Pethidine Hydrochloride* ampoules 100 mg. each : tablets 50 mg. and 100 mg. *Pethidine-Scopolamine* in 2 c.c. ampoules, pethidine 100 mg. and scopolamine 0.43 mg. and *Pethidine-Hyoscine* (pethidine 100 mg. and hyoscine 0.43 mg. or 0.216 mg.).

OPIUM GROUP OF ANALGESICS

| Drug Equivalents | Analgesia | Resp. Depression | Euphoria | Constipation | Addiction |
|---------------------------|-----------|---------------------|----------|--------------|-----------|
| <i>Morphine, 16 mg.</i> | ++++ | ++++ | +++ | ++++ | ++++ |
| <i>Pethidine, 100 mg.</i> | +++ | ++ | +++ | — | +++ |
| <i>Codeine, 30 mg.</i> | ++ | + | + | ++ | ++ |
| <i>Dilaudid, 2 mg.</i> | ++++ | +++ | +++ | +++ | ++++ |

2. **AMIDONE**, dl-2-dimethylamino-4 : 4-diphenylheptane-5-one hydrochloride (Not official) is at least as powerful an analgesic as morphine, toxicity is less, does not cause hypnosis or constipation : euphoria is less common and does not cause addiction : nausea and vomiting are occasional from oral administration only : does not cause contraction of the pupils. It is a **spasmolytic** equalling pethidine.

It is *useful in pain* of malignant disease, in dysmenorrhœa, arthritis, renal colic, pleuritis and in osteomyelitis : may be used for post-operative pain but *not suitable* in obstetrics being depressant to the foetus.

Dose, orally 7.5 to 10 mg. every 3 to 4 hours or *subcutaneously* in smaller doses. The action is manifested in 20 minutes after an injection.

It suppresses *cough reflex* (resembling codeine) and is used in smaller repeated doses for this purpose.

AVAILABLE as *Physeptone*, *Miadone* and *Dolophine* in 5 mg. tablets and 10 mg. ampoules.

3. **PHENADOXONE** is as analgesic as amidone ; orally up to 30 mg. and intramuscularly and intravenously 10 to 20 mg. : may cause addiction.

AVAILABLE as *Heptalgin* 10 mg. tablets or ampoules.

CANNABIS, Cannabis Indica (IND. PHARM. LIST)

GANJA is the flowering tops of the female plant, *Cannabis Sativa*, with the full resin contents.

CHARAS is the resin scarped off from the leaves and flowers.

BHANG (*Siddhi*) is the dried leaf, powdered and made into a drink.

The plant, used as *Bhang*, grows wild almost in all parts of India, but *Ganja* is cultivated in the Rajshahi District of East Pakisthan, under the control of the excise department.

(i) **EXTRACTUM CANNABIS.**—Extracted with alcohol (95%).
Dose, $\frac{1}{4}$ to 1 grain or 0.015 to 0.06 gramme.

(ii) **TINCTURA CANNABIS.**—Extract 1, dissolved in alcohol (90%) 8.
Dose, $\frac{1}{2}$ to $1\frac{1}{2}$ minims or 0.03 to 0.1 ml.

Water precipitates the resin. So it should be suspended with mucilage if prescribed in a mixture.

Pharmacology [and Therapeutics]

The active constituent is a semi-liquid yellowish resin called *cannabinol*.

It is seldom used medicinally and its main use is an **exhilarant** for narcotic purposes. It acts on the *cerebrum* and causes intoxication, remarkable in two ways. First, it excites the imagination more unlimitedly than any other intoxicant: secondly even in the wildest flight of ideas and extravagant imagination, the person is not fully narcotised. He has a dim idea that he is only in a pleasant dreamy state and gives more or less sensible answers when spoken to and is even capable of preforming his routine duties fairly well.

The action generally begins with a feeling of warmth and heaviness in the head. The subject becomes restless and noisy and like an alcoholic, he is less shy and freer in his speech and may even be unmannerly. The action like alcohol, is one of depression of the superior controlling centres and consequent uncontrolled activity of the motor areas. Sooner or later, he sinks into a dreamy condition which is often of a pleasant nature, and he feels to be in greatest psychical and physical well-being. The feeling of pain is lessened and the sense of touch blunted. Time is not estimated correctly, minutes seem to be hours. Intoxication gradually deepens and sleep comes on, from which the patient awakes feeling perfectly well.

Moderate **inhalation** of hemp-smoke or the leaf taken **orally** is said to be refreshing and soothing and barring its constipating action, it may not be definitely injurious. But an excessive dose or frequent habitual indulgence leads to muscular weakness, deterioration of mental capacity and finally to insanity. The **pulse** and **respiration** are quickened, probably as a part of general excitement. But during the stage of deep narcosis, both are slightly slowed. The **pupils** are slightly dilated.

It has the power of relaxing the **spasmodic contraction of plain muscles**, and relieves various kinds of colic in the intestine³⁵⁹⁻³⁶⁰, urinary and gall-bladders and dysmenorrhœa³⁶¹⁻³⁶². It is **constipating** also. It is not used as a hypnotic on account of its uncertain action.

(359) R
Papaver. Hydrochlor. gr. 1
Ext. Cannab. Ind. gr. $\frac{3}{4}$
Ext. Hyoscy. Sicc. gr. $\frac{1}{2}$
Pil. For intestinal colic.

(360) R
Ext. Cannab. Ind. gr. $\frac{1}{2}$
Ext. Opii. Sicc. gr. $\frac{1}{4}$
Gl. Cinnam. min. $\frac{1}{2}$
Pil. For diarrhœa.

INDIAN PHARMACOPŒIAL LIST PREPARATION

RAUWOLFIA (*Sarpagandha, Chandra*), grows wild in Assam, Behar, the Deccan, Pegu, Java and in Malay Peninsula. It contains several alkaloids which are *cerebral, cardiac* and *respiratory sedative*. It is prescribed for **mental sedation** as in insanity (20 to 30 grs. of the powdered root or 8 min. of the liquid extract) and also in smaller doses, for high **blood pressure** and is often helpful in essential hypertension. But it is not altogether free from risk of cardio-respiratory depression and the effect is to be carefully watched for and the dose regulated accordingly.

This is available as *Liquid Extract* (prepared with alcohol 90%, contains 1% of total alkaloids : Dose, 3 to 8 min. or 0.2 to 0.5 ml. *Dry Extract*, contains 4% of alkaloids : Dose, $\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 g. *Tincture*, contains 0.25% of alkaloids : Dose, 12 to 30 min. or 0.8 to 2 ml.

VI. CEREBRAL EXCITANTS

The central nervous system stimulants are a less defined group than the depressants. Thus while the depressants have mostly clearly defined therapeutic applications, (a) many of the stimulants have an after phase of depression also : (b) others have side actions in addition which may complicate their therapeutic application and (c) others again act more on one place than on the other : psychic, motor or medullary stimulants.

In general, the cerebral activities are stimulated by Caffeine, Strychnine, Picrotoxin, Atropine, Camphor, Leptazol and Nikethamide : also by Amphetamine and Ephedrine. In small doses, these cause wakefulness and may either, like caffeine, amphetamine and strychnine, temporarily increase the power of mental concentration or like atropine, camphor and cocaine lead to a state in which the mind wanders actively from one subject to another with diminished power of concentration.

Others as picrotoxin, leptazol and nikethamide are "awakening agents" from a condition of deep narcosis.

With an increased dose, the some of these stimulate the lower centres causing convulsions and the others lead to delirium : others again have specific action on other parts of the body.

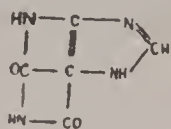
CAFFEINA (*Caffein.*), Theine, Guaranine
 $C_8H_{10}O_2N_4, H_2O$.

Caffeine is an alkaloid obtained from the dried leaves of common tea, *Camellia Sinensis* and also from certain other plants as Coffee, Guaraná, Paraguay tea and Kola nut. It is closely related to theobromine. *Caffeine* is 1 : 3 : 7 trimethyl-xanthine, *theobromine* is 3 : 7 dimethyl-xanthine and *theophylline* is 1 : 3 dimethylxanthine and these may be prepared synthetically from xanthine and are some of the many *purine derivatives*.

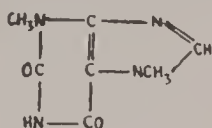
(361) R
 Ext. Cannab. Ind. gr. $\frac{1}{2}$
 Hydrastin. Hydrochlor gr $\frac{1}{2}$
 Ergot. Præp. gr. 1
 Glycer. Trag. q.s.
 Pil. For Menorrhagia.

(362) R
 Ext. Cannab. Ind.
 Pulv. Opii aa. gr. $\frac{1}{2}$
 Camphora. gr. 2
 Glycer. Trag. q.s. (Lucus).
 Pil. For dysmenorrhœa.

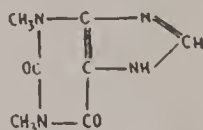
Colourless, inodorous, silky, acicular, crystals but with a bitter taste and efflorescent in dry air : soluble 1 in 80 of water and 1 in 40 of alcohol (90%). If to the watery solution, $\frac{1}{2}$ gr. of sodium salicylate is added for each grain of caffeine, the solution is complete.



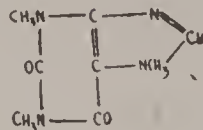
Xanthine



Theobromine



Theophylline



Caffeine

Tea grows in Assam, Darjeeling, Ceylon, China and in Japan.

Dose, 5 to 10 grains or 0.3 to 0.5 gramme,

INCOMPATIBLES.—Salts of mercury, potassium iodide and tannic acid.

Caffeina et Sodii Benzoas (*Caffein. et Sod. Benz.*).—Prepared by mixing equal parts of caffeine and sodium benzoate, moistening with water or alcohol and drying. It contains between 47 to 50% of anhydrous caffeine and 50 to 53% of sodium. A white inodorous powder, with slightly bitter taste. Soluble in 4 parts of cold and in 1 of hot water ; feebly so in alcohol (90%).

Dose, 5 to 15 grains or 0.3 to 1 gramme and 2 to 5 grains or 0.12 to 0.3 gramme by subcutaneous injection.

Injectio Caffeinæ et Sodii Benzoatis (*Inj. Caffein. et Sod. Benz.*), See p. 43.

Dose, 2 to 5 grains or 0.12 to 0.3 gramme. If strength is not stated, about $3\frac{3}{4}$ gr. in 15 min. or 0.25 g. in 1 ml. shall be dispensed.

1. THEOBROMINA ET SODII SALICYLAS (*Theobrom. et Sod. Salicyl.*), Theobromine and Sodium Salicylate, Diuretin.

This is obtained by mixing sodium hydroxide, theobromine and sodium salicylate in molecular proportion and should be preserved in amber coloured glass-stopped bottles.

This a white amorphous powder with no smell and sweetish alkaline taste : freely soluble in water but insoluble in alcohol (90%), chloroform and solvent ether. It contains 46% theobromine, $C_7H_5O_3N_4$ and 41% sod. salicylate, $C_7H_5O_3Na$ and 6.9% of sodium.

Dose, 10 to 20 grains or 0.6 to 1.2 gramme.

2. THEOPHYLLINA (*Theophyll.*), $C_7H_8O_2N_4H_2O$.

Theophylline, 1 : 3 dimethylxanthine, is an alkaloid, obtained from the dried leaves of *Cammelia Sinensis* or prepared synthetically.

A white inodorous crystalline powder with a bitter taste : soluble in 120 parts of water at 25°C. and more so in hot water : soluble in 80 parts of alcohol (90%) at 25° and sparingly so in solvent ether.

Dose, 1 to 3 grains or 60 to 200 mg.

Injectio Mersalyli (*Inj. Mersalyl.*), See p. 44. It contains in 30 minims, 3 grs. of mersalyl and 1.5 grs. of theophylline.

Dose, 8 to 30 minims or 0.5 to 2 ml. by intravenous or intramuscular injection.

3. THEOPHYLLINA ET SODII ACETAS, (*Theophyll. et Sod. Acet.*), Theophylline and Sodium Acetate, Theocine Sodium Acetate.

Prepared by dissolving equimolecular proportions of sodium theophylline and sodium acetate in water and evaporating to dryness : a white, crystalline, inodorous powder with a bitter taste. Contains not less than 55% of anhydrous theophylline, $C_7H_8O_2N_4$. Soluble at 15.5° in 25 of water but insoluble in alcohol (90%), solvent ether and in chloroform

Dose, 2 to 5 grains or 0.12 to 0.3 gramme.

4. THEOPHYLLINA CUM ÆTHYLENEDIAMINA, (*Theophyll. c. Æthylenediam.*), Aminophylline, Cardophyllin, Euphyllin.

Prepared by dissolving theophylline in ethylenediamine and evaporating to dryness. White or yellowish white granules with slightly ammoniacal odour and bitter taste. This should contain 71·5 to 78·5% theophylline, $C_7H_8O_2N_4$ and 11·8 to 13·2% ethylene diamine, $C_2H_8N_2$. Soluble at 25°, in about 5 parts of water : insoluble in dehydrated alcohol and in solvent ether.

Dose, $1\frac{1}{2}$ to 8 grains or 0·1 to 0·5 gramme.

Injectio Theophyllinæ cum Æthylenediamina (*Inj. Theophyll. c. Æthylenediam.*), See p. 48.

Dose, $1\frac{1}{2}$ to 8 grains or 0·1 to 0·5 gramme by intramuscular or intravenous injection. If the strength is not stated, 8 gr. in 30 min. (0·5 g. in 2 ml.), for intramuscular and 4 gr. in 150 min. (0·25 g. in 10 ml.) for intravenous injection shall be dispensed.

Pharmacology [and Therapeutics]

The three alkaloids, **caffeine**, **theobromine** and **theophylline** are all purine derivatives and are allied to one another. Of these, *caffeine* acts powerfully on the central nervous system : *theophylline* is a powerful diuretic and coronary vessel dilator but *theobromine* is less active, and acts on the muscles, to a less extent, on the heart and the kidneys, little on the cerebrum.

Caffeine preparations have three important actions.—

(i) These excite the *central nervous system*, especially the superior psychic centre and to some extent, the medulla.

(ii) These increase the force of contraction of *all muscle fibres*, striped, unstriped and cardiac.

(iii) These are *diuretic*.

TAKEN INTERNALLY.—The alkaloid caffeine is absorbed readily, with very little local action on the stomach. It is absorbed well from the subcutaneous injection also. But taken in the form of tea and coffee, on account of the large amount of tannin and some volatile oils contained in them, there is some local action also on the stomach. The volatile oil gives the flavour but tannin causes **constipation** and if taken in large quantity on the empty stomach and frequently, it causes gastric irritation : the appetite becomes poor, ultimately resulting in dyspepsia.

CENTRAL NERVOUS SYSTEM.—Caffeine in *therapeutic doses*, stimulates the whole of cerebrum especially the **psychic** and the **sensory functions**, largely resembling that of strychnine on the spinal cord (q.v.). It facilitates the perception of sensory stimuli as well as the **association of ideas**. The *mental activity* is increased, the feeling of drowsiness and fatigue disappears, the *reflex functions* are quickened and there is response to weaker stimuli. Ideation becomes clearer and quicker and more sustained intellectual efforts become possible. The acuteness of the *senses* is also increased. But recently acquired motor skill requiring delicate and co-ordinate muscular movements may be interfered with (Horst, 1934).

This exalted reception of the sensory impressions and association of ideas, especially marked during fatigue, are not as readily transformed into excessive movements: this is thought to be due to simultaneous stimulation of the controlling function of the highest centres of the brain which restrains unnecessary movements, a condition exactly opposite to action of alcohol (Kraepelin).

Caffeine is usually taken in the form of morning tea or coffee to drive away the remnant of night's sleep and in the evening to combat drowsiness after fatigue.

Further, it increases the **capacity** for performance of all kinds of **physical work** and the power of **endurance**.

It is also used as an **antidote to narcotic poisoning** causing coma as that by morphine poisoning.

In large doses the stimulation passes on to the motor areas. It causes restlessness, headache, insomnia, confusion of thought and stimulation of some of the sense organs, shown by the appearance of flashes of light before the eyes and noises in the ears. The reflexes are increased and the limbs often show spasmodic movements. The latter action is more marked in animals and may ultimately terminate in convulsion.

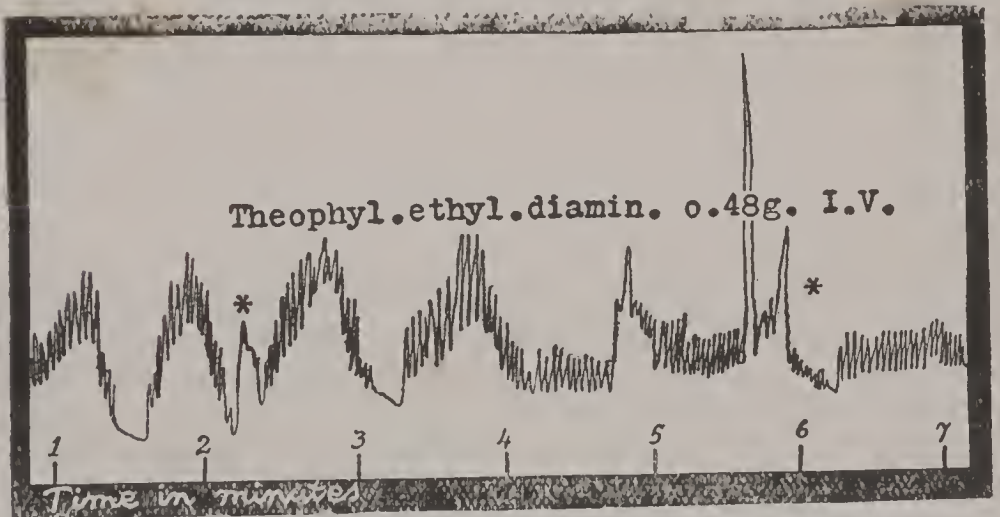


Fig. 32.—Effect of Theophylline ethyl diamine on the respiratory centre: the drug is given very slowly intravenously between the two * * marks. Cheyne-Stokes breathing is regularised but is of low amplitude.

MEDULLA is also excited: there is a certain amount of **slowing of the pulse** (vagal centre) and **vaso-constriction** (vaso-motor centre), more of the limbs than of the viscera and also decided stimulation of **respiration** increasing the rate but not so much the depth as increased ventilation lessens the CO_2 -contents of the blood causing a comparatively shallower breathing. These are more marked when caffeine and sodium benzoate is given hypodermically. [Caffeine is often prescribed parenterally in narcotic poisoning but picrotoxin and nikethamide are better].

Dyspnoea of cardiac origin and Cheyne-Stokes respiration improve under aminophylline.

SPINAL CORD.—With a therapeutic dose, the reflexes are slightly exaggerated but toxic doses may cause tetanic convulsions of spinal origin.

In lower animals, an injection of a large dose of caffeine markedly increases the reflex excitability, leading to convulsions resembling those caused by strychnine, the action in them being thus more marked on the spinal cord than on the brain.

Thus there is some similarity between the action of caffeine and strychnine, both acting on the nerve cells: caffeine acts mainly on the *upper division* of the nervous system activating psychic centre and strychnine on the *lower* mainly augmenting the reflex functions.

To sum up: Caffeine increases the reflex irritability, which begins in the **psychic areas** and with a small dose, this is the only part of the cerebrum appreciably affected. With a bigger dose, it extends downwards to the **medullary centres** (respiratory, vaso-motor and vagal). With a still bigger dose, **motor area** is also stimulated and restlessness ensues: with a toxic dose, the **spinal cord** is affected shown by increased reflexes and finally convulsion.

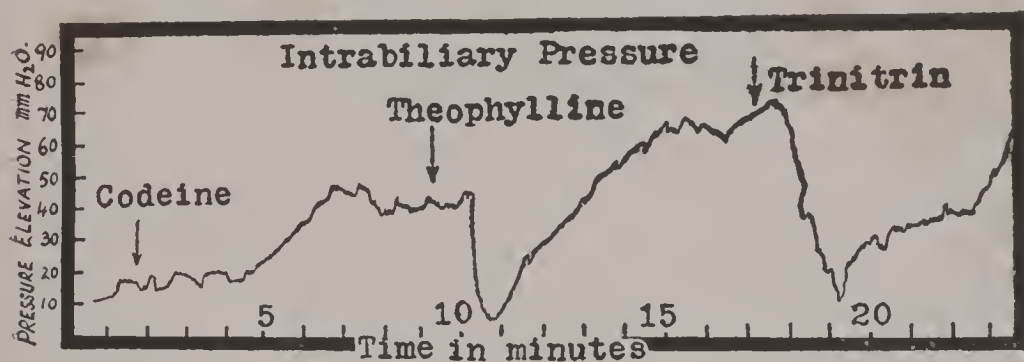


Fig. 33.—The effects of codeine, theophylline and trinitrin on intrabiliary pressure are shown. Codeine causes contraction, theophylline, relaxation and trinitrin, even greater relaxation of the bile duct.

MUSCLE TISSUE.—It has a specific action on all forms of muscle tissue, the striped, unstriped, and cardiac. (a) With a *small dose*, the **contractility** and total strength of the **striped muscles** are increased, especially during fatigue. In addition to the central action on the nervous system which is more important, the muscles are directly stimulated and contract more completely and powerfully with weaker stimuli and against a greater load. Thus the total work that the muscles can do is increased. This action is equally marked with theobromine which has no action on the central nervous system. (b) But in *toxic doses*, the working capacity is lessened and if a solution of caffeine is applied directly on a piece of muscle tissue, this becomes stiff on account of coagulation of myogen.

The **unstriped muscles** in spasmodic state is *relaxed*. This action is best marked with theophylline. Biliary passages contracted by an injection of morphine are **relaxed** by

theophylline ethyldiamine. Similar effect is produced on the bronchioles in asthma^{363, 364}.

CARDIAC MUSCLE AND THE CIRCULATION.—With a *small dose* of about 5 grains, caffeine has not much action on the human heart but a bigger dose as 8 to 15 grains moderately increases the cardiac output without any change in the pulse rate. But in some individuals showing marked stimulation of central nervous system, caffeine increases the pulse rate, blood pressure and cardiac output.

A *big dose* given intravenously to an animal, the heart rate is markedly quickened from direct action on the heart muscles.

As caffeine causes this acceleration even when both the acceleratory and the inhibitory nerves are cut, this must be a direct action on the muscles.

With *still large doses*, this accelerating action is more marked and as the pulse rate is very much quickened, the cardiac output diminishes and the blood pressure falls. Finally, the sinus rhythm is lost: spontaneous impulses are produced, first in the auricles and then in the ventricles. Afterwards the auricular fibrillation starts followed by that of the ventricles and death.

Blood Vessels.—After a brief period of vaso-constriction from the stimulation of the centre in medulla, **all blood vessels dilate**. As this is due to the direct action on the muscle, it affects even those without vaso-constricting nerves, as the pulmonary, cerebral and the coronary vessels.

Dilatation of the coronary blood vessels becomes obvious when either caffeine, theobromine or theophylline is perfused through an isolated heart and theophylline seems to act best.

Blood Pressure falls only slightly or there is no fall at all, the effects of vaso-dilatation being counterbalanced by increased efficiency of the cardiac muscles. But with a big dose, when the pulse rate is much increased, the cardiac output diminishes and the blood pressure falls.

ALIMENTARY CANAL.—Caffeine and theobromine in small doses have no action. Vague discomfort and loss of appetite may sometimes be complained of probably from action on the gastric mucous membrane. This is more marked with theophylline, even small doses may be causing minute hæmorrhages and erosion. Caffeine tends to increase the gastric acidity for a prolonged period and may sometimes be contributory to causation of gastric ulcer.

(363) R
Caffein. Tri-iod. gr. 2
Ephed. Hydrochlor. gr. $\frac{1}{2}$
Ext. Bellad. Sicc. gr. $\frac{1}{4}$
Glycer. Trag. q.s.
Pil. For asthma.

(364) R
Aminophyllin. gr. 2
Phenobarbiton. gr. 1
Ephed. Hydrochlor. gr. $\frac{1}{2}$
Glycer. Trag. q.s.
Pil. For asthma.

KIDNEYS.—The secretion of *urine* is decidedly increased mainly involving the fluid portion and this is of low specific gravity. Because the quantity is increased, the *total excretion of solids*, both as regards salts especially sodium chloride and to a less extent, urea and uric acid are also increased. This diuresis is mostly due to (a) dilatation of the renal vessels without any fall of blood pressure though owing to the preliminary vaso-constriction, this action is slightly delayed.

(b) Caffeine is also believed to increase the functioning surface of the glomerular epithelium (Richards), bringing into use a larger number of glomeruli and probably to some extent, to lessen tubal resorption, allowing more rapid filtration through the kidneys.

(c) Sodium chloride factor is also important. This is withdrawn from the tissues to accumulate in the circulating blood. This increases non-colloidal contents and also blood volume causing diuresis. Increased fluid volume dilutes the urinary acid and this along with increased excretion of alkalies makes the urine almost neutral in reaction.

Increased volume of urine draws fluid from the blood and blood volume is restored from the tissues. If any pathological collection of fluid exists, this is removed. If not, fluid is abstracted from the stomach and the intestine causing a sensation of thirst.

But as a diuretic, it is inferior to theobromine and theophylline is most active: further, caffeine causes cerebral excitement and sleeplessness which makes it unsuitable for therapeutic use as diuretic in many cases.

METABOLISM.—It slightly increases the metabolism, the amount of CO_2 and urea excretion being increased.

EXCRETION.—This takes place in the urine. About 10% of caffeine is destroyed in the tissues and is made successively into dimethyl and monomethyl-xanthine, xanthine and finally into urea; the rest is excreted partly unchanged but mostly made into xanthine compounds.

TOLERANCE.—The habitual use, usually in the form of tea or coffee leads to a certain amount of tolerance probably from lessened response and increased destruction.

[To SUM UP.—

Caffeine is a useful drug, frequently prescribed for its action as a **cardiorespiratory stimulant** either for a weak, decompensated heart or in an emergency when the circulation or the respiration is failing or seriously embarrassed as in narcotic poisoning³⁶⁵.

(365) B

Caffein. gr. 20

Sod. Salicyl. gr. 17½

Aq. Steril. min. 120

For hypodermic injection in 10 to 15 min. doses.

Cardiac and respiratory stimulant and diuretic.

It is often prescribed for **dropsical conditions**³⁶⁶ especially of **decompensated heart disease** and may be combined with **digitalis**. It is of less value in the **œdema of chronic kidney diseases**. On account of renal congestion caused, it is unsuitable in the acute affection of the kidneys.

Its power to **relieve fatigue** and to act as a cerebral stimulant makes tea such a valuable beverage. For the same reason, strong tea or coffee is given in narcotic poisoning. It is also useful in **migraine**³⁶⁷, and is often combined with analgesics like **phenacetin**. It is also of some value in **bronchial asthma**].

Theobromine

It is an alkaloid, obtained from cocoa. It has no stimulating action on the central nervous system but acts more powerfully than **caffeine** in increasing the efficiency of the heart, dilating the coronary, renal and peripheral arterioles and causing better diuresis. Because of its insolubility, it is prescribed as the soluble double salt made in combination with **sodium salicylate**, called *Diuretin*, or as **sodium sodioacetate salt**, *Agurin*.

It acts as a powerful **diuretic**³⁶⁸. Its action is best exhibited in a case of **œdema of congestive heart failure**, especially if combined with **digitalis**. In **chronic kidney diseases** also it is frequently effective and produces diuresis without increasing the renal damage but it is contraindicated in **acute nephritis**.

On account of vascular dilatation, it does not raise the blood pressure. It sometimes **relieves cardiac pain** by dilating the coronary arteries. [It is therefore useful in some cases of **angina pectoris** and **arteriosclerosis with hypertension**: it is profitably combined with a small dose of **phenobarbitone (luminal)** and often given at bedtime for the relief of nervous excitement and insomnia.

Theophylline, Theocine

It is often used as **theocine sodium acetate**. It is the most powerful **diuretic**³⁶⁹ of this group and is fairly popular especially in **cardiogenic œdema**. But it causes more gastric

(366) R
Pot. Cit. gr. 15
Caffein. Cit. gr. 3
Tinct. Digit. min. 10 to 15
Decoc. Agropy. ad. fl. oz. 1
(Lucus).

For cardiac dropsy.

(367) R
Caffein. gr. 5
Phenacetin. gr. 5
Amidopyrin. gr. 4
Cachet. For migraine.

(368) R
Sod. Iod. gr. 3
Diuretin gr. 5
Pot. Acet. gr. 20
Aq. Chlorof. ad. fl. oz. 1
For cardiac and chronic nephritic œdema.

(369) R
Pot. Acet. gr. 15
Theocin. Sod. Acet. gr. 3
Inf. Buchu. Rec. fl. oz. 1
2 to 3 times daily for general anasarca.

irritation and sometimes upsets digestion and may cause hæmorrhagic erosions and is known to have produced convulsions.

In the post-mortem examination, minute hæmorrhages have been found in the gastric mucous membrane.

[Combined with mersalyl it is given intramuscularly or intravenously in cardiac or hepatic dropsy: ammonium chloride, 60 to 120 grains, is also given orally daily at the same time: the advantages of combination of mercury with theophylline are (a) toxic ionisable mercury compounds are not liberated and (b) combined effect causes greater diuresis].

It has some reputation as **dilator of coronary blood vessels** [and is helpful in coronary insufficiency].

Aminophylline, Theophylline ethylene diamine

Being more soluble than theophylline base, aminophylline is quicker in action. This augments the renal circulation and is thus a better **diuretic** and **coronary vessel dilator**. It causes a certain amount of *peripheral vaso-dilatation* also. The result is a stimulating effect on both normal and failing heart, more marked in hypertensive disease than in mitral stenosis. It reduces the venous pressure also. It causes **broncho-dilatation** and stimulation of the **respiratory centre** increasing the rate and depth of respiration. It may be given orally, intramuscularly or for immediate action, intravenously (with glucose solution): rectal suppository is also used. [This is used in cardiac oedema, angina pectoris, coronary thrombosis and cardiac asthma³⁷⁰]. It is also of value in *barbiturate poisoning* as cardio-respiratory analeptic. This should not be used in acute nephritis. It tends to increase **coagulation of blood** (and is of value in hæmoptysis).

It is used in **bronchial asthma**³⁷¹ also. Being chemically related to histamine and antihistamine drugs, aminophylline 0.375 g. in 10 c.c. very slowly intravenously has been found useful in many allergic conditions (Turner, 1949). It is also of value in chronic **Cheyne-Stokes respiration**.

Occasionally an intravenous injection may cause *alarming symptoms* even death in gross myocardial degeneration and coronary occlusion but is safe in uncomplicated asthma and controls the paroxysm (Leon Unger 1944). Sometimes adrenaline-refractory cases of status asthmaticus may be relieved by slow intravenous injection of 0.25 to 0.5 g. of aminophylline in

(370) R

Aminophyllin.

Phenobarbiton.

Papaver. Hydrochlor.

aa. gr. 1½

Mucil. Acac. and Trag. q.s.

Pil. One at bed time.

(371) R

Aminophyllin.

Phenobarbiton. aa. gr. 1½

Ephedrin. Hydrochlor. gr. ¼

Mucil. Acac. and Trag. q.s.

Pil. One at bed time.

10 c.c. of isotonic saline : relief may be due to broncho-dilatation and pulmonary vessels dilatation.

COMMERCIALLY available as *aminophylline*, *aminocardol*, *cardophyllin*, *minaphil* and *phylcardin*, in 0.1 gm. tablets orally ; also ampoules of 0.48 gm. intramuscularly, 0.24 gm. intravenously and suppository 0.15 gm. and 0.36 gm. per rectum.

SUMMARY.—*Caffeine* stimulates the **psychic centre**, relieves fatigue and increases muscular power : it also stimulates the **respiratory centre** and may be helpful parenterally in respiratory failure. *Theobromine* is a diuretic (useful in congestive heart failure and in chronic nephritis) and **vaso-dilator** (useful in hypertension and angina pectoris). *Theophylline* is a more powerful diuretic (used as inj. mersalyl or as aminophylline) : **vaso-dilator** (used in hypertension and angina pectoris) and **broncho-dilator** (used in asthma).

Non-official Preparations

CAFFEINE CITRAS, caffeine citrate.—This is a white powder having an acid taste and reaction and is frequently used orally. It is soluble in 32 of water but with sodium salicylate it forms a bulky precipitate.

Dose, 2 to 10 grains or 0.12 to 0.6 gramme.

CAFFEINE SODIUM SALICYLATE in 1 to 4 grains doses is given by the mouth and subcutaneously.

CAFFEINE TRI-IODIDE, (Dose, 2 to 4 grains), given in rheumatism, asthma and in gout.

KOLA, the tincture and the wine are used in 30 to 60 min. doses.

CELERINA, a patent medicine, is said to contain cocoa, celery, kola and viburnum. Both are prescribed as restorative in nervous exhaustion.

THEOBROMINE CALCIUM SALICYLATE, Calcium-diuretin. (Theobromine 48% and calcium salicylate 11%). Dose, 5 to 15 grs. (Slightly soluble in water).

ODO-CALCIUM DIURETIN (Dose, 2 to 10 grs.), relieves vascular spasm and is useful in asthma, high blood pressure and in angina pectoris.

DERIPHYLLIN (Theophylline, diethanolamine and adonis vernalis) and **DERIMINAL** (Theophylline, diethanolamine, adonis vernalis, phenazone and phenobarbitone) are used in angina pectoris, cardiac asthma, cardiac oedema, hypertension, migraine and in bronchial asthma.

Dose, 0.5 to 2 c.c. i.v. or i.m. and 20 min. orally.

THEOMINAL, **THEOGARDINAL**, a combination of theobromine 5 gr. and luminal or gardenal $\frac{1}{2}$ gr. : useful in angina pectoris and arterio-sclerosis with nocturnal dyspnoea and insomnia.

THEOBROMINE-SODIUM-ACETATE, (Agurin). Dose, 10 to 15 grs. (hygroscopic, given in solution), used as a diuretic.

DIGI-CARDINE has digitoxin 0.05 mg. and aminophylline 50 mg. in tablet is useful in congestive heart failure, cardiac asthma and auricular fibrillation.

SEDO-CARDIAL and **SEDOPHIL** tablets have aminophylline and phenobarbitone are useful in nocturnal dyspnoea.

B. Drugs Acting on the Sub-Thalamic Region

In health, heat is *produced* in the body by the normal activities of different muscles and glandular structures and it is *lost* by radiation from the skin and the lung-surface and also with the excreta. These two are so regulated that in health the body temperature is maintained at a constant level with morning and evening variations of near about one degree. If from any cause heat loss is above normal, the skin blood vessels contract and the muscles get into clonic contraction

(chill and rigor) and more heat is produced with diminished loss. If the source of heat production is excessive muscular efforts, the loss is also proportionately increased. The cutaneous blood vessels dilate, the respiratory rate increases and so also the secretion of sweat. All these bring down the temperature to the normal level again. This adjustment of the body heat is controlled by a centre in the basal ganglia near the tuber cinereum.

If the temperature rises rapidly in disease (fever), this rise is often preceded by a feeling of chill and even rigor. The cutaneous vessels are constricted (restricting the loss of heat) and the muscles are thrown into contraction so as to raise the internal temperature quickly. High temperature is one of the methods of defence of the body against any foreign invasion and therefore with a severe infection a comparatively low temperature is of ominous prognosis, indicating inability of the body to put up a good defence.

So long as the temperature keeps high, the condition is one of increased heat production and diminished heat loss, that is to say, the heat regulating centre is adjusted at a higher gear.

Although Cocaine, Belladonna and Picrotoxin in toxic doses and β -tetrahydronaphthylamine raise the body temperature, these are never used for any therapeutic purpose.

PYRETOTHERAPY

In certain diseases as in neurosyphilis and gonorrhœa, high temperature as upto 104°F has a curative value. In certain chronic infections and inflammations also a similar treatment is useful.

For therapeutic purpose the temperature is raised to 103° or 104°F in 3 to 4 hours and kept up for about 8 hours. The following means are employed.—

(i) *Malaria therapy*.—Blood from a patient with benign tertian parasites is injected intravenously (2 c.c.) or intramuscularly (5 c.c.). This causes fever in two weeks and about 6 paroxysms are allowed.

(ii) *Protein shock therapy*.—Typhoid-paratyphoid vaccine, milk protein and rarely tuberculin are used intravenously or intramuscularly.

(iii) *Intramuscular injections* of drugs as colloidal sulphur and sodium nucleinate.

(iv) *Physical agents* as hot bath and hot beddings also diathermy and other electrical methods of raising the heat.

The optimum rise of temperature can be accurately regulated by the last group only and are getting more popular.

ANTIPYRETICS

ANTIPYRETICS are drugs that can lower the body temperature. In health no drug lowers the normal body temperature except with a dose that may induce almost dangerous collapse. But cold applications or some drugs are at times useful in many febrile conditions especially if the temperature is high. These favour an increased loss of heat acting peripherally or centrally. These are as follows :

(i) *Cold application* to the body as an ice-cap on the head, cold sponging and cold bath. The loss of heat is by direct abstraction from the skin : but this does not immediately lower the blood heat very much on account of cutaneous vaso-constriction and lessened radiation. Yet these are undoubtedly helpful measures.

Further, from the skin reflex, pulse and the respiration are stimulated to be fuller and more accelerated. Unless the cold application is very prolonged, it is free from any harmful after-effect and is a safe and frequently used method of lowering the raised body temperature.

(ii) *Vaso-dilators*.—The most important is tepid sponging. The skin vessels dilate favouring a greater radiation of the body heat : this is more often liked by patients than cold sponging and the effect, although immediately less obvious, is more lasting.

Drugs like pilocarpine although causing profuse secretion of sweat, are not used as diaphoretic for therapeutic lowering of the body temperature.

Alcohol, by dilating the peripheral blood vessels, causes a moderate fall in the skin temperature, but as it increases the metabolism and internal combustion, the total loss is not very much and so is not a good antipyretic.

Opium as Dover's powder is a mild diaphoretic. Benzoates may be also included here.

Diaphoretics, especially many of the salts of Sodium, Potassium and Ammonium and *vaso-dilators* as Spirit of nitrous ether are favourite ingredients of a fever mixture.

Salicylates may also be included in this group, which reduce temperature by causing vaso-dilatation and sweating. But these and cinchophen are more *definitely antipyretic* in acute rheumatic fever. These are *analgesic* also.

(iii) Some antipyretics act by *diminishing the metabolism* : Quinine is sometimes put in this group. But its antipyretic activity is apparent mainly in malarial fever by its specific chemotherapeutic action.

(iv) Some of these act directly on the *heat-regulating centre* in the brain-stem. General anæsthetics by depressing the centre are temporary antipyretics but more lasting effects are produced by the coal-tar antipyretics as Acetanilide, Phenazone, Phenacetin and Amidopyrine. As these relieve pain also, these are called *analgesic antipyretics*.

ANALGESIC ANTIPYRETICS

These have two main groups : (i) phenacetin, phenazone and amidopyrine and (ii) salicylates and cinchophen.

1. PHENACETINUM (*Phenacet.*), Acetophenetidin,
 $C_{10}H_{13}N_2O$.

Phenacetin is aceto-*p*-phenetidine, prepared by the acetylation of *p*-phenetidine. It is in white glistening crystalline tasteless scales or powder : soluble in 1700 of water : in 21 of alcohol (90%) and freely soluble in solvent ether, chloroform and glycerin. It does not liquefy with sodium salicylate.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

OFFICIAL PREPARATIONS.—(i) *Tabellæ Phenacetini* (*Tab. Phenacetin.*), See p. 57. Strength is 95 to 105% of phenacetin. Dose, as of phenacetin. (ii) *Tabellæ Acidi Acetylsalicylici et Phenacetini* (*Tab. Acid. Acetylsalicyl. et Phenacetin.*), Aspirin and phenacetin tablets. See p. 56. Dose, 1 to 2 tablets. (iii) *Tabellæ Codeinæ Compositæ* (*Tab. Codein. Co.*), See p. 57. Dose, 1 to 2 tablets.

2. PHENAZONUM (*Phenazon.*), Antipyrin, $C_{11}H_{12}ON_2$.

Phenazone is 1-phenyl-2 : 3-dimethyl-5-pyrazolone, prepared by the interaction of phenylhydrazine and ethyl acetoacetate and subsequent methylation.

White or colourless crystals or white crystalline powder having no smell but a bitter taste and is freely soluble in 1.2 parts of water, 1.3 parts of alcohol (90%) and chloroform and 1 in 50 of solvent ether.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

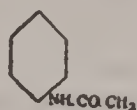
It is *incompatible* with so many substances that it should better be prescribed alone : liquefies with sod. salicyl.

Tabellæ Phenazoni (*Tab. Phenazon.*), See p. 57. Each contains if not otherwise stated, 5 grains. Strength is 95 to 105% of phenazone.

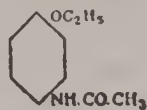
Dose as of phenazone.

3. AMIDOPYRINA (*Amidopyrin.*), Pyramidon, $C_{13}H_{17}ON_3$.

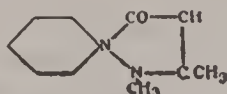
Amidopyrine is 4-dimethylamine-1-phenyl-2 : 3-dimethyl-5-pyrazolone, prepared by methylation of the reduction product of the nitroso derivative of phenazone. Colourless crystals or white crystalline powder with no smell and very little taste.



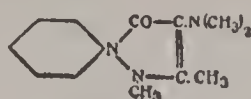
Acetanilide



Phenacetin



Phenazone



Amidopyrine

Soluble in 18 of water, in 2 of alcohol (90%) and readily so in solvent ether, chloroform and benzene.

Dose, 5 to 10 grains or 0.3 to 0.6 gramme.

ACETANILIDUM, Antifebrin, C_8H_9ON (Not official).

Prepared by heating glacial acetic acid with aniline and then distilling it. Colourless glistening crystals with a pungent taste.

It is soluble 1 in 200 of cold water, 1 in 4 of alcohol (90%) and freely in chloroform and ether.

Dose, 2 to 5 grains.

Pharmacology [and Therapeutics]

These antipyretic drugs were mostly discovered while attempting to prepare quinine synthetically. In 1884 phenazone was first prepared by Knorr and acetanilide (1886), phenacetin (1887) and others have followed since.

Earlier preparations as phenazone (antipyrin) and acetanilide (antifebrin) were comparatively toxic. Other compounds prepared with hydrogen of the hydroxyl substituted by an alkyl group and an acid radicle added to the amino radicle. Thus phenacetin was prepared which was found to be more satisfactory.

The antipyretics now in use act by forming simple derivatives of para-aminophenol in the tissues. The quicker the change takes place, the greater is the toxicity (shown by destructive changes in the blood cells and tendency to collapse) and the antipyretic action is less sustained. Therapeutic efficiency and safety are thus mainly dependant on this property of slow transformation.

APPLIED EXTERNALLY, the drugs of this group have no action. Like other drugs of the coal-tar group, these are **antiseptic** but are not as active as phenol or salicylic acid and therefore are not used as such. Acetanilide and Phenazone are feeble **hæmostatics**.

TAKEN INTERNALLY, Phenacetin and its derivatives are *slowly* decomposed into paraminophenol and their action therefore is more lasting and the toxicity is less severe. Given in big doses, these change oxyhæmoglobin in the *red cells* into *methæmoglobin*. But this seldom happens with phenazone.

Therapeutically these drug are mostly used as **antipyretics** to lower the temperature when it is high in fever. This is done (i) by acting on the *heat-regulating centre*. This action is rapid and is seldom delayed beyond 2 to 3 hours and is not manifested in an individual with normal temperature. In fever, this centre is set at a high gear and more heat is produced than lost. These drugs may act by increasing the resistance of the centre to the poison of the disease, so that the centre is *adjusted to a lower gear* at which the temperature is now maintained. Further, the heat loss is also increased.

Thus the action of the antipyretics on the heat-regulating centre is antagonistic to the same of the fever-producing toxin.

That these act through the heat regulating centre in the basal ganglia is proved in the following way :

(a) They do not very much lower the temperature in health when the heat-regulating centre is at the normal gear (except in doses causing dangerous collapse).

(b) If the basal ganglia is separated from the rest of the body by cutting through the spinal cord fairly high, neither can a diseased process raise the temperature nor these antipyretics lower it, when so raised.

But if the section is made above the basal ganglia and the temperature is raised, these antipyretics can lower it.

(c) A lesion near about the basal ganglia raises the temperature and these antipyretics given orally, or in a much smaller quantity applied directly, lower the temperature.

(d) If in a dog with moderate fever (temperature 40.9°) is given an antipyretic and temperature brought down to 37.6° , attempts to raise the temperature by heat application often fails : by dissipating the extra heat, the temperature is maintained near about 37.6° (Stern and Richter).

(ii) The cutaneous *blood vessels* are moderately dilated causing a red flush and favouring increased radiation of heat. So the temperature comes down, partly by diminished production and partly by increased loss of heat.

(iii) The lowering of temperature by these drugs is very often associated with *profuse sweating*. But the main action is upon the centres since these are yet antipyretic even if sweating is prevented by atropine. Occasionally, the antipyretic effect may be profound, especially if several repeated doses are given. The temperature may then go much below normal, resulting in collapse.

(iv) *Metabolism* is lowered during their administration shown by, lessened oxygen absorption and nitrogen elimination but this is the *effect* of a lower temperature but not the *cause*.

But as the drugs are rapidly absorbed and excreted, the effects are short-staying.

[In practice, these are often used in mild catarrhal fevers attended with marked headache, pain in the limbs and running from the nose^{372, 373}. These act not only by reducing the temperature, but being analgesic also, greatly promote the comfort of the patient by lessening the pains and aches and making him quiet and sleepy. In prolonged fevers, like typhoid fever or pneumonia, these are usually considered dangerous but may be given in fevers of shorter duration for the relief of malaise and pain, usually as phenacetin, in 2 to 3 grains doses twice or three times daily, especially during the height of fever. The general vascular depression is insignificant, the temperature is reduced by 1 to 2° , tissue metabolism is lessened and there is a feeling of comfort.

For reducing the temperature in tuberculosis³⁷⁴, these are more frequently used. These not only give a mental relief to

(372) R

Aspirin gr. 3

Camphora gr. $\frac{1}{2}$

Phenacetinum. gr. 3

Lactosum gr. 10

Pulv. For coryza.

(373) R

Aspirin. gr. $3\frac{1}{2}$

Phenacetin. gr. $2\frac{1}{2}$

Caffein. Cit. gr. 1

Pulv. : Popular A.P.C.

(374) R

Phenacet. gr. 3

Cryogenin. gr. 2

Atrop. Sulph. gr. 1/200

Lactosum gr. 10

For fever in tuberculosis.

the patient that he is nearly fever-free and is getting better but also make him more comfortable].

CEREBRUM.—This is somewhat depressed resulting in quietening down of the nervous irritability and restlessness. These drugs have considerable power of lessening pain also, (**analgesic**), especially headache and pain of neuralgia or neuritis, by raising the threshold at which a stimulus is capable of causing pain. [These are frequently prescribed for various painful conditions, especially for headache and muscular pain].

The action is not on the cortex but probably lower down, it may be on the *optic thalamus* or somewhere in the synapses of the path conveying the sense of pain.

These are **not strongly hypnotic** and do not produce somnolence if the patient is up and about; if taken at bedtime these favour the onset and maintenance of normal sleep. *Cortical cells* are slightly depressed but even in large doses, these are not much depressant to the intellectual centres. This distinguishes them markedly from morphine, bromides and other central depressants.

Phenacetin, being an ethyl compound has more powerful cortical action: *Phenazone* is least so but is more **depressant** to the **motor areas** [so that it has been prescribed³⁷⁵ in epilepsy, chorea, dysmenorrhœa and whooping cough (conditions associated with uncontrolled motor activity), sometimes with benefit].

Amidopyrine acts more slowly and the effects are more lasting. This is comparatively less harmful to the heart and the kidneys. [This is advocated in the treatment of measles. In a favourable case, the temperature comes down more quickly and with less complications and distress].

Continued for sometime, it causes **leucopenia** and some cases of **agranulocytic angina** recently described, associated with fever, ulceration in the throat and marked leucopenia with high death rate are probably caused by it. This is thought to be due to its toxic action on the bone-marrow.

Several commercial preparations contain Amidopyrine with a barbiturate. The combination intensifies the analgesic effect. (See p. 499).

MEDULLARY CENTRES are scarcely affected, if at all. In poisonous doses, these cause convulsions probably by stimulating the cerebral and sometimes the spinal centres and perhaps also from asphyxia. **PERIPHERAL NERVES** are not appreciably affected.

(375) B

Phenazon. gr. 5

Pot. Brom. gr. 10

Ammon. Bicarb. gr. 1

Syr. Tolu min. 60

Aq. Chlorof. ad. fl. oz. $\frac{1}{2}$

For whooping cough.

CIRCULATION.—With a comparatively small dose, the most constant effect is a certain amount of **vaso-dilatation** but no definite depression of the heart muscles. Yet these drugs have acquired a bad name of being circulatory depressant. In laboratory experiment, the **heart muscles** of the animal are directly stimulated by a small dose causing temporary acceleration but bigger doses depress them and the heart beat becomes slow and irregular leading to collapse. The **blood pressure** is lowered.

Collapse is sometimes seen, more profound with acetanilide especially when given in bigger doses but when it occurs from moderate doses, it seems to be due to idiosyncrasy. Nearly all the fatal cases are from taking large doses of patent headache cures frequently. These contain caffeine in addition as the latter is a heart stimulant. But Worth Hale has shown that these are more toxic with caffeine than without and less so with sodium bicarbonate.

But if taken in moderate doses and not frequently repeated, these are fairly safe. Of these, phenacetin is the least, and acetanilide, the most toxic. So the former is more commonly used. [These are often given in dysmenorrhœa, myositis³⁷⁶, headache, especially migraine^{377, 378}, sciatica and other kinds of neuralgia³⁷⁹ or peripheral neuritis]. The danger is that a tolerance is soon established and in order to produce the effect, these are taken in increasing doses above the safe limit and toxic symptoms follow.

EXCRETION.—These are rapidly excreted by the kidneys and disappear within 24 to 30 hours. The urine having their oxidation products, may take up reddish-brown colour.

TOXIC MANIFESTATIONS.—(i) There may be gastro-intestinal irritation resulting in vomiting and purging.

(ii) Collapse, especially in a sensitive and weak individual when a large dose is taken. The pulse becomes small and irregular, temperature sub-normal, the patient becomes drowsy and cyanosed. The last is partly due to feeble heart action and partly from the formation of methæmoglobin in the blood. Antifebrin (acetanilide), is most liable to cause these toxic symptoms.

(iii) Red blotchy skin eruptions, sometimes measly or scarlatinal: catarrh with burning pain in the mouth and throat, œdema of the mucous membrane of the mouth and also of the eye-lids may follow, especially after antipyrine.

(376) R
Veganin: *Codopyrin*
 Aspirin.
 Phenacet. aa. gr. 4
 Codein. Phosph. gr. ½
 Tablet. For pain.

(377) R
 Phenacet. gr. 5
 Quinin. Salicyl. gr. 4
 Lactosum gr. 10
 Pulv. For migraine.

(378) R
 Acetanilid. gr. 2½
 Ammon. Carb.
 Sod. Bicarb. aa. gr. 1½
 Lactosum gr. 10 (Guy's)
 Antineuralgic.

(379) R
 Phenacet.
 Phenazon. aa. gr. 4
 Exalgin gr. 1
 Cachet. For neuralgia.

Although phenacetin is less poisonous, in large doses it may cause sleepy state followed by convulsions, cyanosis and collapse.

(iv) Agranulocytosis may sometimes result from amidopyrine.

Other drugs causing agranulocytosis are sulphonamides, thiouracil, gold salts, organic arsenicals, dinitrophenol and certain other toxic chemicals.

SUMMARY.—*Phenacetin*, *Phenazone* and *Amidopyrine* act on the sub-thalamic regions reducing the temperature of fever (antipyretic) and relieving pain especially headache, neuralgia and muscular pain (analgesic). *Phenazone* is a motor relaxant also. These cause vaso-dilatation and sweating and unless taken in big doses or too frequently repeated, these are not particularly harmful.

Non-official Preparations

NOVALGIN (sodium phenyl-dimethyl-pyrazolon-methyl-aminomethane-sulphonate), in $7\frac{1}{2}$ grains tablets, is given 2 or 3 times daily for many painful conditions. The solution in ampoules is given in dose of 1 to 2 c c. subcutaneously, intramuscularly or intravenously.

LACTOPHENIN.—A powerful analgesic. Dose, 5 to 15 grains.

EXALGIN, (Dose, $\frac{1}{2}$ to 2 grains).—This is more powerful and is given for neuralgia and sometimes with success when other drugs fail. But should not be continued long and the dose should never exceed 2 grains.

PHENALGIN, (Dose, 5 to 20 grains).—Antineuralgic-antipyretic.

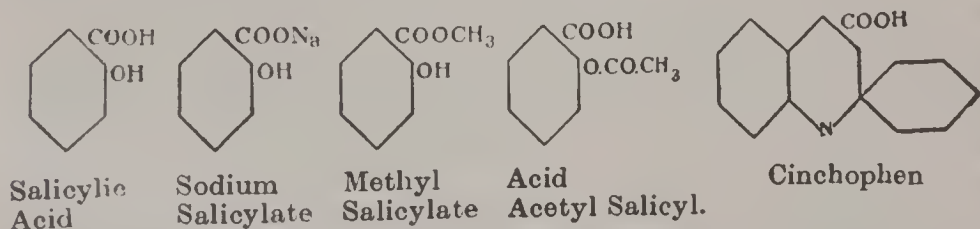
ANTI-KAMNIA, contains acetanilide 7, caffeine and soda bicarb. 2. Dose, 3 to 5 grains.

SALIPYRIN, (Antipyrine salicylate). Dose, 15 to 30 grains is antipyretic and analgesic.

SARIDON.—Phenacetin 4 gr., phenyldimethyl iso-propyl pyrazolon $2\frac{1}{2}$ gr., sedormid $7\frac{1}{8}$ gr. and caffeine $\frac{3}{4}$ gr. made into tablet.

ACIDUM SALICYLICUM (*Acid. Salicyl.*), $C_7H_6O_3$

Obtained from natural salicylates as oil of winter-green, *Gaultheria procumbens* or the oil of sweet birch, *Betula lenta*; the B.P. directs it to be synthetically prepared by the interaction of sodium phenate and CO_2 . It should contain not less than 99.5% of $C_7H_6O_3$.



It occurs in colourless and inodorous prismatic, crystals or light feathery crystalline powder with a sweetish and acid taste, soluble 1 in 500 of cold and 1 in 150 of hot water: soluble 1 in 3.5 of alcohol (90%). Freely soluble in solvent ether, chloroform, solutions of ammonium acetate, potassium citrate, sodium phosphate and of sodium citrate.

INCOMPATIBLES.—Iron and quinine salts and spirit of nitrous ether, aromatic spirit of ammonia and spirit of nitrous ether.

Unguentum Acidi Salicylici (*Ung. Acid. Salicyl.*), See p. 62. (2%).

1. SODII SALICYLAS (*Sod. Salicyl.*), $NaC_7H_5O_3$.

Sodium salicylate obtained by the interaction of salicylic acid and sodium carbonate. It is also prepared from the natural salicylates. It contains not less than 99.5% of $C_7H_5O_3Na$ of the substance dried at 110° .

It occurs in colourless flakes or pearly tabular crystals or white powder with sweetish saline taste. Soluble in 1 of water and in 6 of alcohol (90%).

DOSE, 10 to 30 grains or 0.6 to 2 gramme.

INCOMPATIBLES.—Iron and quinine salts, acids and antipyrine.

Tabellæ Sodii Salicylatis (*Tab. Sod. Salicyl.*), See p. 58.

DOSE as of sod. salicyl. Each Tablet, if not otherwise stated, contains 5 grains.

2. ACIDUM ACETYLSALICYLICUM (*Acid. Acetylsalicyl.*), Aspirin, $C_9H_8O_4$.

Prepared by the interaction of salicylic acid and acetic anhydride or acetyl chloride. This is a white crystalline inodorous powder with a slightly acid taste. It contains not less than 99.5% of $C_9H_8O_4$. Exposed to moist air, it slowly decomposes into acetic and salicylic acids and should be kept in a well-closed container. Aspirin is yet a trade name in some places.

Soluble at 15.5° in about 300 parts of water, in 5 of alcohol (90%), 20 of solvent ether, 17 of chloroform and in strong ammon. acetate solution. Dissolves in alkalis with decomposition.

DOSE, 5 to 15 grains or 0.3 to 1 gramme.

(i) **Tabellæ Acidi Acetylsalicylici** (*Tab. Acid. Acetylsalicyl.*), See p. 56. Contains between 94 to 105% of $C_9H_8O_4$.

DOSE, the same as of the above : each tablet contains, if not otherwise stated 5 grains of acetylsalicylic acid.

(ii) **Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio** (*Tab. Acid. Acetylsalicyl. c. Ipecacuanha et Opio*), See p. 56.

(iii) **Tabellæ Acidi Acetylsalicylici et Phenacetini** (*Tab. Acid. Acetylsalicyl. et Phenacetin.*), See p. 56.

(iv) **Tabellæ Codinæ Composita** (*Tab. Codein. Co.*), See p. 57.

SALICINUM, Salicin, $C_{11}H_{16}O_7$ (Not official).

It is a crystalline glucoside obtained from the bark of various species of *Salix* and *Populus*.

Soluble 1 in 28 of cold water and 1 in 80 of alcohol (90%) and insoluble in ether and chloroform.

DOSE, 5 to 15 grains or 0.3 to 1 gramme.

This is the earliest preparation of this group (Laroux, 1827) : Piria, (1838), prepared salicylic acid from this. Salicylic acid was synthesised from phenol by Kolbe and Lautemann, (1860).

3. METHYLIS SALICYLAS (*Methyl. Salicyl.*), Methyl Salicylate, Artificial oil of winter green, $C_8H_8O_3$.

Prepared artificially by the esterification of salicylic acid with methyl alcohol containing not less than 98% of C_2H_5O .

It is a colourless or pale yellow liquid with a characteristic aromatic smell and sweetish, warm taste. It is only slightly soluble in water but freely in alcohol (90%).

LINIMENTUM METHYLIS SALICYLATIS (Not official).—Menthol 50 g., oil of eucalyptus 100 ml., rectified oil of camphor 250 ml. and methyl salicylate to make 1000 ml.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, Salicylic acid originally introduced as a substitute for phenol, is an **antiseptic**, but it is less irritant and less penetrating. Like quinine it stops the activity of unicellular protoplasm and enzymes. Applied to the skin or the mucous membrane in a concentrated form, it causes

corrosion and **superficial tissue-necrosis**. [It is therefore sometimes used dissolved in collodion or made into a plaster for removing warts³⁸⁰. The horny layer of the epidermis is softened and slowly separated as a white pellicle without causing any inflammation or pain]. In more dilute form, it is a local **astringent** (and is sometimes made into dusting powders for checking excessive perspiration³⁸¹. It is also used in **skin diseases**³⁸² associated with thickening of the skin as in chronic ringworm³⁸³.

The action is mainly due to its acidity and the neutral salts are feebly antiseptic and are not used externally. *Methyl salicylate* or the oil of winter green is quickly absorbed when rubbed into the skin. It is an irritant causing **counter-irritation** and **analgesia**, the common property of all salicylates and is a common ingredient of various liniments³⁸⁴.³⁸⁵. It is also used as a **flavouring agent** in mouth washes and in tooth pastes. It is hardly used internally.

TAKEN BY THE MOUTH, a neutral salt like *sodium salicylate* has very little irritant action on the stomach but as a part of it is changed into salicylic acid by hydrochloric acid, given in big doses it may cause **gastric irritation** and **vomiting** and is often prescribed with sodium bicarbonate. It has mild **antiseptic** action and may control gastric fermentation. *Acetylsalicylic acid* is not so decomposed and is well borne by the stomach : but taken on empty stomach, it may cause irritation and even minute hæmorrhages in the gastric mucous membrane : if taken frequently, it may cause gastritis. An old sample sometimes undergoes spontaneous decomposition into acetic and salicylic acids giving the characteristic acetic acid smell. Such a sample more often causes gastric irritation and should be discarded.

Gastric irritation caused may be avoided by giving 4 grains of acetyl salicylic acid with 2 grains of colloidal aluminium hydroxide, available as *Alasil tablets* : 4 to 6 tablets may be tolerated at a time.

(380) R
Acid. Salicyl. gr. 40
Ext. Cannabis Ind. gr. 5
Colloid. Flex. ad. fl. oz. 1
(Lucas).

Corn solvent.

(381) R
Acid. Salicyl. gr. 20
Zinc. Oxid. gr. 10
Acid. Boric. gr. 200
Pulv. Amyl. gr. 120
Talc. oz. 1

Pulv. For perspiration of hands
and feet.

(382) R
Acid. Salicyl. gr. 10
Sulphur. Sublim. gr. 15
Paraff. Moll. Alb. oz. 1

Ung. For chronic seborrhœa
capitis.

(383) R
Acid. Salicyl. gr. 120
Alcohol (90%) fl. oz. 1
A paint on a ringworm patch
once daily for 2 days.

(384) R
Menthol gr. 2
Ol. Camph. Rect. min. 120
Ol. Eucalyp. min. 60
Methyl. Salicyl. min. 120
Ol. Arach. ad. fl. oz. 1
A stimulating liniment.

(385) R
Menthol 4
Methyl. Salicyl. 15
Eucalyptol 1
Adeps Lan. Hydros. 45
Paraff. Moll. Alb. 35
An analgesic cream.

ABSORPTION and ELIMINATION.—Most of the salicylic acid preparations are rapidly absorbed and mostly changed into sodium salicylate in the blood. It accumulates in the plasma, to a less extent in the corpuscles and appears in nearly all secretions of the body, but less so in the cerebro-spinal system. It is believed to slightly increase the quantity and the fluidity of the **bile** [and is combined with big doses of hexamine in an alkaline mixture to drain and disinfect a septic gall-bladder].

About 70% of the salicylates is *excreted unchanged* by the kidneys. A part is oxidised to dioxybenzoic acid and hydroquinone and is partly excreted in combination with sulphuric and glycuronic acids. Although it appears in the urine in less than an hour of its administration, about 48 hours are necessary for complete elimination. The urine tends to become acid, resulting in feeble **urinary disinfection**. Sodium salicylate excreted unchanged reduces Fehling's solution and may be mistaken for sugar in the urine. Sometimes the urine becomes dark green in colour from excretion of these oxidised substances. A small fraction is also excreted in the *sweat, milk and bile*. About 20% of it is *destroyed* in the tissue in health and more so in acute rheumatic fever.

Given in bigger doses, the salicylates **irritate the kidneys** causing albuminuria and scanty urine. The quantity of urine may be temporarily increased but more often diminished: this is partly due to loss of fluid by diaphoresis and partly by direct action on the kidneys. So when big doses of salicylates are given, any sign of renal irritation should be carefully looked for.

METABOLISM.—These temporarily increase the **general metabolism** (may be 20 to 25%) and the excretion of urea, sulphates and chlorides in the urine; so also of **uric acid** even with a purine-free diet: this increase may be 30 to 50% or higher resulting in a fall in blood uric acid and rise in urine uric acid. The **alkali reserve** of the blood is slightly lowered. This is probably due to altered tissue metabolism and accumulation of lactic and phosphoric acids in the blood and also probably to diminished elimination by the kidneys.

TEMPERATURE.—The salicylates are slightly **antipyretic** in simple catarrhal fevers: act by dilatation of the skin vessels and perspiration causing increased loss of heat. These act on the thermogenetic centre in the hypothalamus. The B.P. Aspirin and Dover's powder tablet is a suitable preparation. No such action takes place in a healthy afebrile person: there the heat-loss is counterbalanced by increased heat production.

But this antipyretic effect is most pronounced in **rheumatic fever**. [Given in big doses as 20 grains of sodium salicylate three hourly, usually about one grain per pound body weight daily, the temperature rapidly falls and the pain in the joints also quickly subsides³⁸⁵. To prevent a relapse, the dose is

reduced gradually and continued for some time. Early treatment with adequate doses of salicylates may prevent many of the complications of rheumatic fever.].

A blood plasma level of 30 to 40 mg.% of the salicylate is usually necessary : this requires about 10 g. daily. The relapse or remission often occurs with a fall or rise in the salicylate level in plasma. When sodium bicarbonate is also given at the same time, the elimination of the salicylate is increased and this causes a fall in the plasma level. The treatment should be maintained by keeping a watch on the plasma and urine salicylate concentration level and appearance of symptoms of intolerance as tinnitus, deafness, nausea, vomiting (these usually happen when plasma level reaches or exceeds 35 mg.%), requires administration of an adequate dose of sodium bicarbonate.

Acetyl salicylic acid is well-tolerated if given with aluminium hydroxide³⁸⁷ ; 6 to 8 doses one every 3 hours (about 128 mg./kg. daily) till nearabout the 3rd day the adequate plasma level is reached with marked clinical improvement : then this may be given every 6 hours or less frequently. Calcium aceto-salicylate is also effective and well tolerated. These are **better analgesic** than the sodium salt.

PERSPIRATION, a common accompaniment, is partly due to vasodilatation and partly to stimulation of the sweat centre : therapeutically a salicylate mixture is a suitable **diaphoretic**.

CIRCULATION.—In therapeutic dose, sodium salicylate is **not depressant** to the heart. A blood level upto 0.12% of the salicylate is harmless (Friderichsen). Formerly synthetically prepared samples contained orthocresotic and paracresotic acids which were toxic and cardiac depressant. But pure salicylates are now available and the natural salicylic acid is free from any depressant action. Given in therapeutic doses, **the heart beat is slightly quickened** probably from action on the heart muscles. But if the dose much exceeds the limit, the heart beat becomes slow and weak.

The **blood pressure** is slightly raised by a small dose from stimulation of the **vasomotor centre**. But a dose above the therapeutic limit, lowers the pressure by depressing the centre as well as the heart muscles.

In therapeutic doses, it tends to **lessen capillary transudation** and this may be one of the reasons for rapid relief of swelling and pain of *rheumatic arthritis* : sometimes it helps absorption of pathological effusion from the *serous cavities*.

(386) R
Sod. Salicyl. gr. 20
Sp. Chlorof. min. 15
Syr. Aurant. min. 60
Aq. Aneth. ad. fl. oz. 1
Every 2 to 4 hours in rheumatic fever.

(387) R
Acid. Acetyl. Salicyl.
Alocol. aa. gr. 10
Pulv. Trag. Co. gr. 7½
Aq. Chlorof. ad. fl. oz. 1
Every 2 to 4 hours in rheumatic fever.

A 20 to 40% solution had been used by injection for *sclerosing a varicose vein*: any fluid escaping into the surrounding tissues may cause local tissue necrosis.

RESPIRATION.—With a moderately big dose, respiration is quickened and deepened may be causing slight dyspnoea: pulmonary ventilation may be increased. These are due to direct stimulation of the centre or/and may be from some substance obtained from the salicylates. With bigger doses, respiration may be slow and feeble and tidal air below normal. Death follows from respiratory failure.

NERVOUS SYSTEM.—It is an **analgesic** of moderate intensity probably acting on the thalamus. This effect is intensified in combination with codeine and phenacetin, (See p. 521). The **medulla** is slightly stimulated, resulting in slight quickening of respiration, a moderate degree of vasoconstriction and rise of blood pressure. But with a bigger dose, sodium salicylate causes circulatory and respiratory depression.

For *therapeutic administration*, sodium salicylate and acetyl salicylic acid are most popular and much more frequently used than any other salicylate. Acetyl salicylic acid or *Aspirin* is more commonly used for the relief of pain³⁸⁸. This passes through the stomach unchanged and is partly decomposed in the intestine into acetic and salicylic acids and absorbed. A part of it is also absorbed direct. In addition to the usual salicylic action, it is a powerful **analgesic**. The portion absorbed unchanged is probably responsible for this action. In a susceptible person, it may cause allergic manifestations as asthma, urticaria and fall in blood pressure appearing quickly after administration. *Salicin* is changed into salicylates in the system. It has feeble salicylate action³⁸⁹ and is not so irritant to the stomach but it is not as frequently used as sodium salicylate.

TOXIC MANIFESTATIONS.—If given in big doses or as an after-effect of prolonged administration, especially in people susceptible to it and if the plasma concentration exceeds 30 mg.%, there may be toxic symptoms mainly on the central nervous system. These are disturbances of vision and hearing as in cinchonism (fullness in the head, deafness, ringing in the ears and dimness of vision), also headache and delirium: anorexia, vomiting, diarrhoea: depression of the heart, fall of blood pressure, excessive sweating, skin rashes and bleeding from mucous surfaces (lowered prothrombin concentration) with feeble pulse and subnormal temperature. In more severe cases, there may be collapse and hypoprothrombinæmia and death from paralysis of the respiratory centre. These are called "*Salicylism*". Acetylsalicylic acid sometimes causes œdema of the eyelids, lips, pharynx and of the limbs, less commonly urticaria and rarely asthmatic attacks.

(388) B

Acid. Acetyl. Salicyl. gr. 4
Phenacet. gr. 2
Camphora gr. 1
Pulv. Ipecac. et Opii gr. 3
Pulv. For coryza.

(389) B

Salicin gr. 10
Camphor. gr. 1
Ipecac. Pulverat. gr. $\frac{1}{2}$
Pulv. In the beginning of influenza

Treatment.—Further administration of the salicylate is at once stopped and a plenty of soda bicarbonate with 4 pints of fluid administered daily. Haemorrhagic state requires the administration of vitamin K.

SUMMARY.—*Salicylic acid* is used externally as **keratolytic** and **astringent** and *Methyl salicylate* as **analgesic** in liniments. *Sodium salicylate* is mainly used in **rheumatic fever** usually 1 gr. dose per pound body weight daily for 2 or 3 days (when pain and temperature subside) and then less frequently for some days: toxic symptoms are to be watched for. This and more so *Acetylsalicylic acid* are used as **analgesic**. These also act as **diaphoretic** in coryza and increase the **bile flow**.

Non-official Preparations

SALOL ($C_{13}H_{10}O_3$), Phenyl salicylate, prepared by the interaction of salicylic and carbolic acids. It contains 60% of salicylic acid and 40% of phenol. The crystals are colourless with a slight aromatic odour: practically insoluble in water and soluble 1 in 15 of alcohol (90%) and also in fixed and volatile oils^{390, 391}.

DOSE. 5 to 20 grains or 0.3 to 1.2 grammes.

OLEUM GAULTHERIE, oil of Winter Green, distilled from the leaves of *Gaultheria procumbens* or the bark of *Betula lenta*, which grow in North American colonies. The Indian variety *G. fragrantissima* (*Gandapuro*), grows in Assam, Burma and Travancore. The oil is either colourless or slightly yellow with a characteristic odour. This is in **IND. PHARM. LIST**.

DOSE, 5 to 15 minims or 0.3 to 1 ml.

TYLCALSIN (Calcium aceto-salicylate), **DOSE**, 5 to 15 grains, is soluble in water, analgesic and antipyretic and may be more tolerated in rheumatic fever. **ASPRIODINE** (Acetyl iodo-salicylic acid). **DOSE**, 6 grains after food. **SALIGENIN** (**DOSE**, 10 grs.). Used for painful conditions.

SALIPYRIN, (Antipyrin salicylate), **ACETOPYRIN** (Antipyrin acetosalicylate). **DOSE**, 10 to 15 grains, insoluble powders given for acute and chronic rheumatism.

IRGAPYRIN, a pyrazol with amidopyrine in 5 c.c. ampoules for intramuscular injection at 1 to 2 days' interval: for acute and chronic arthritis: 4 to 6 injections are necessary.

CINCHOPHENUM (*Cinchophen.*), Quinophan, Atophan

This is 2-phenylquinoline-4-carboxylic acid, prepared by the interaction of pyruvic acid and benzylideneaniline. It contains not less than 99% of $C_{16}H_{11}O_2N$, dried in a vacuum desiccator over sulphuric acid.

White or yellowish powder or crystals with no smell but slightly bitter taste. Insoluble in water but soluble in 120 of alcohol (95%), in 100 of solvent ether, in 400 of chloroform and in solutions of alkaline hydroxides, carbonates and bicarbonates.

DOSE, 5 to 10 grains or 0.3 to 0.6 gramme.

Pharmacology [and Therapeutics]

Cinchophen resembles the salicylates in being *analgesic* and *antipyretic*. In addition, it favours the *excretion of uric acid* especially if this is high as in gout.

(390) R

Salol 2.5

Saccharin 0.004

Ol. Menth. Pip. 2

Alcohol (80%), 97

This resembles *Odol*, used as mouth wash.

(391) R

Salol gr. 5

Benzonaphthol. gr. 4

Bism. Carb. gr. 15

Pulv. For summer diarrhoea.

Although colchicine has the remarkable property of quickly relieving pain of a gouty joint, it does not favour the elimination of the excess of uric acid from the blood which is responsible for the disease.

Attempts were being made for a long time to find out something that would do so. Large doses of alkalies, hexamine and piperazine dissolve uric acid outside the body but these, given to a gouty patient, do not augment the elimination of urates. Salicylates moderately increases both the formation and elimination of uric acid. Cinchophen is the only drug so far found to substantially increase the elimination.

Cinchophen has been found of much therapeutic value in the treatment of **Chronic gout**. Uric acid (up to 0.003%), is present in normal blood and even with a purine-free diet some of it remains. This comes from the normal tissue katabolism. In gout, the uric acid level reaches high. To such a patient, Cinchophen being given acts within 3 hours : a large amount of uric acid is excreted in the urine and that in the blood falls. A fresh room is thus made in the latter for the tissue urates to come over and in this way by keeping up the elimination high, the tissue urates, from their collection in various gouty deposits are drained out.

In many cases, the blood uric acid is not lowered : may be even above normal in spite of increased elimination. This is due to increased elimination of urates from a pre-existing store and increased formation uric acid therefrom with its rapid removal.

With continued administration, the excretion comes down to normal in 2 to 3 days unless the diet contains purines. Uric acid level in blood consequently falls but it soon reaches an irreducible minimum, there being no further lowering even if the administration of the drug is continued for several days.

Perhaps the kidneys are acted on directly : probably these are made more permeable to urates and the normal tubal re-absorption is also hindered. But the excretion of other constituents of the urine is not markedly increased though in some cases of retention, urea and chlorides are excreted in larger quantity.

Cinchophen, especially neo-cinchophen, is mildly **antipyretic**, **antineuralgic** and like salicylates, **antirheumatic**. But the dose required to be effective is not always within safe limits.

Cinchophen is mostly decomposed in the tissues but a part of it is excreted in the urine unchanged.

Toxic Symptoms may appear with prolonged administration, especially in big doses, such as anorexia and other digestive disturbances, degenerative changes in the liver even acute yellow atrophy : also anaphylactoid reaction, vertigo, cardiac distress and various types of skin eruptions especially urticaria. These are probably due to hepatic insufficiency or disturbed kidney functions.

If the urine is previously made alkaline, these toxic symptoms do not usually appear.

Further, as eliminated uric acid in hyperacid urine may form gravels, alkalisation of the urine is essential.

MODE OF ACTION is yet uncertain. Grabfield and Gray found that cinchophen increases total nitrogen, sulphur, allantoin and uric acid elimination. This is markedly lessened by denervation of the kidneys and by ergotoxine thus showing that the action is through adrenergic fibres.

[Cinchophen is given in 20 to 30 grains doses daily for 3 to 4 days, along with double the amount of sodium bicarbonate in a mixture, for chronic gout, gouty diathesis, sub-acute and chronic rheumatic affections, sciatica and similar other painful conditions and often with much benefit. An interval of about 4 days is given and then the drug is repeated again. As individual idiosyncrasy exists, the drug in the beginning should preferably be given in even smaller doses.

Non-official Preparations

NEOCINCHOPHEN, NOVATOPHAN or TOLYSIN.—This is the ethylester of methyl-cinchophen : an insoluble pale yellow powder ; given in the same dose as above. This is nearly tasteless and non-irritant to the alimentary canal and better tolerated.

ATOPHANYL, is a mixture of equal parts of sodium atophan and sodium salicylate. A solution of 0.5 gm. each in 10 c.c. available in ampoules, is given intravenously.

ANOTAL, (Ethylurethane of phenylbenzopyridincarboxylic acid) in 5 grs. tablets, 4 to 6 tablets are given daily for gout.

ATOQUINOL is cinchophen allyl ester is less gastro-intestinal irritant (0.5 g. tablets and 20% ointment).

PIPERAZIN (Diethylene-diamine), in 5 to 15 grs. and **SIDONAL** (Quinino-anhydride), in 7½ grs. doses, are sometimes given for various conditions of uric acid diathesis : not very dependable.

GUAIACUM LIGNUM (Guaiacum Wood).—The active substance is a resin. This gives a bitter acid taste to the mouth and the throat which is continued down into the epigastrium as a burning feeling. It acts as a stomachic and carminative and has some reflex stimulating action on heart, but in very big doses, it is a gastro-intestinal irritant. It was formerly prescribed for chronic joint troubles and dysmenorrhœa but as it has no dependable action, it is now-a-days seldom used for any purpose.

ANALGESICS

Analgesics are drugs that *relieve painful sensations without causing loss of consciousness*. The action may be (a) **central**, namely on the sensory centre in the brain, or subthalamie region : (b) or the sensory **nerve terminations** in different parts of the body.

1. DRUGS ACTING ON THE SENSORY CENTRE.

(i) *Opium alkaloids* as morphine, codeine, dilaudid and diamorphine : *synthetic preparations* as pethidine and amidone (physeptone) act centrally, and a dose that relieves pain, does not usually affect the other centres in the brain and may

not cause any loss of consciousness. These frequently used, tend to cause some tolerance and often drug habit.

SCOPOLAMINE-MORPHINE ANÆSTHESIA.—A sort of semiconsciousness is obtained by subcutaneous injection of 1/200 grain of Scopolamine and 1/6 grain of Morphine hydrochloride and is given for lessening the painful sensations of child-birth. The injection requires repetition in smaller doses on complaining of pain. This combination is also used as pre-anæsthetic medication.

SCOPOLAMINE-PETHIDINE ANÆSTHESIA is also used for obstetric amnesia; 100 mg. of pethidine and 0.3 mg. of scopolamine is the initial dose: total dose in 18 hours must not exceed 400 mg. of pethidine and 1.3 mg. of scopolamine. (See p. 523).

(ii) Coal-tar analgesics.—These include Acetanilide, Phenacetin, Phenazone, Amidopyrine also Acetyl-salicylic Acid (aspirin) and to some extent, Cinchophen. These relieve neuralgia and headache. The action is central: this is not in the cortex but probably at the sensory synapses near the optic thalamus.

Colchicine relieves pain of gout and cinchophen also to some extent relieves pain in the muscles and nerves in gouty diathesis.

General anæsthetics, causing complete unconsciousness, are analgesics but are not included here.

(iii) Cannabis Indica.—This also to some extent relieves pain by lowering the general sensibility of the brain very much like the alcohol-group. But it is not as effective.

VENENUM NAJÆ (Cobra Venom), IND. PHARM. LIST, is standardised to contain in one mg. of the dry powder not less than 50 mouse units. Dose, 1 to 3 mouse units, the initial dose: subsequent doses, 5 to 25 units in gradually increasing doses: given intramuscularly is analgesic by acting on the pain centre. The action is slow and several daily injections have to be given: 0.001 mg. is used for painful carcinoma: also sometimes used in *epilepsy* and *asthma*.

2. DRUGS ACTING ON THE SENSORY NERVE-ENDINGS.

These drugs are used as local applications on the painful areas as lotions, liniments or plasters: also by injections.

Although opium is made into liniments or plasters and applied on the skin to relieve pain, it does not penetrate through the intact skin and is of doubtful value.

The most dependable local anæsthetics are drugs of the *Cocaine group*. These are mostly given hypodermically or applied directly on the various mucous membranes for surgical purposes and sometimes for the relief of pain also.

Recently, procaine in 0.1% in 5% glucose solution has been given by *slow intravenous drip* as 20 to 30 drops per minute with total dose 4 mg./kg. of body weight, with favourable result in many painful and vaso-spastic states.

Benzyl alcohol is of some value.

Ethyl chloride in spray causes superficial freezing and local analgesia.

Ether evaporating causes some anæsthesia.

Quinine urethane is a local anæsthetic by hypodermic injection.

Belladonna group.—These are rubbed into the skin with alcohol, glycerin or fat, so as to reach the sensory nerve-endings to have the action.

Menthol.—At first it stimulates the sensory nerve-endings, mostly those carrying the cold sense and then paralyses them and relieves pain.

Phenol is also a local anæsthetic.

Aconite.—At first it stimulates the terminations of the sensory nerve-fibres, shown by tingling followed by paralysis-anæsthesia. As it is very poisonous if absorbed, care should be taken in its use in liniments which is not to be rubbed in.

Butyl-chloral-hydrate, *Gelsemium*, and *Conium* are sometimes used for neuralgia but are of doubtful value in therapeutic doses. *Chlorbutol* is a local anæsthetic on the mucous membrane.

Magnesium sulphate.—Given parenterally, it at first paralyses the central then the peripheral sensory nerve-endings (p. 212) and is injected or applied locally on a wound surface in many painful conditions including tetanic spasms and carbuncle.

All *rubefacients* act as analgesic indirectly by relieving the local vascular congestion and are the commonest constituents of liniments, used for the relief of superficial pain.

C. Drugs Acting on the Medulla

The medulla is the most vital part of the nervous system.

(a) It has through the vagus nerve, the centres for *circulation* and *respiration* and also of *gastro-intestinal movements*. Drugs that excite the medulla cause slowing of the pulse, rise of blood pressure, increased respiratory rate, cough, vomiting and purging.

(b) The *cardio-acceleratory centre* is also in the medulla but this is not affected by the usual medullary excitants except by cocaine. This is however stimulated by a peripheral stimulus as by painful affections or electric shock, irritation of the nose (as by ammonia) or throat and stomach (as by alcohol or an ammonia solution). A profound stimulus on the contrary causes depression.

The drugs acting on the medulla do not affect all the centres simultaneously and have a certain amount of selective affinity either for one or the other. Thus, Apomorphine acts mainly on the vomiting centre (in smaller doses on the cough centre) whereas Morphine, on the respiratory and Digitalis on the cardiac centre. Strychnine, Caffeine, Leptazol and Nikethamide excite the respiratory, cardiac and the vasomotor centres.

Drugs acting on the respiratory and cardio-vascular centres of the medulla may roughly be grouped as follows :—

Respiratory Centre

Ammonia, Co_2 + +
 Strychnine, Caffeine + +
 Leptazol, Nikethamide + +
 Picrotoxin + +
 Cocaine, Camphor +
 Turpentine + —
 Lobeline + + —
 Apomorphine + —
 Cyanides + —
 Veratrine + —
 Nicotine + —
 Atropine + —
 Aconite, Hydrocyanic Acid—
 General anæsthetics, narcotics—
 Opium—
 Physostigmine—
 Gelseminine, Coniine—
 —indicates depression.

Cardiac and Vaso-motor Centres

Digitalis group +
 Strychnine, Caffeine +
 Suprarenal and Posterior
 Pituitary extracts +
 Leptazol, Nikethamide +
 Ephedrine, Amphetamine +
 Co_2 , Ammonia +
 Camphor + —
 Turpentine + —
 Local irritants + —
 Atropine + —
 Physostigmine + —
 Hydrastis, Veratrine + —
 Nicotine + —
 Aconite, Hydrocyanic Acid—
 Chloral Hydrate—
 General anæsthetics—
 + indicates stimulation.

It will thus appear that there is no separate cardiac or respiratory central stimulants : the drugs that stimulate one in most case do the same to the other. They are consequently called *analeptics*.

Most of these drugs have other systemic actions also and are described elsewhere.

1. PICROTOXINUM (*Picrotox.*), Cocculin, $\text{C}_{30}\text{H}_{34}\text{O}_{13}$

Picrotoxin is a glycoside obtained from the seeds of *Anamirta paniculata*. Flexible, shining inodorous. prismatic crystals or microcrystalline powder : effected by light, soluble at 15.5° in 334 of water and in 35 of boiling water : 13.5 of alcohol (90%) : more easily soluble in diluted acids and alkalies but only slightly in ether and chloroform.

DOSE 1/100 to 1/20 grain or 0.6 to 3 mg.

Injectio Picrotoxini (*Inj. Picrotox.*) is a sterile solution of picrotoxin in water for injection, sterilised by autoclaving or by filtration.

DOSE, as of Picrotoxin by intravenous or intramuscular injection. If the strength is not stated, one containing 3 mg. in a ml. shall be dispensed.

Pharmacology [and Therapeutics]

Picrotoxin in a human being acts mainly on the *central nervous system* and causes **convulsion**. At first salivation, sometimes vomiting, with quickening of respiration and slowing of the heart with palpitation commence (medullary stimulation) followed by stupor and unconsciousness ; these pass on to convulsion, at first tonic and then clonic with alternate extension and flexion of the limbs (as distinguished from prolonged tonic contraction of strychnine poisoning). There are periods

of short pause and finally fatal end may follow from respiratory failure.

Commencing from a frog to human being, it appears that the seat of action moves upwards to higher parts of the central nervous system. Thus in a *frog* it is mainly the spinal cord, medulla and the optic lobes and in *mammals*, **cerebrum** and **midbrain**. Probably the action in a *human being* is mostly in the cerebrum.

Medullary stimulation causes slow pulse (vagal inhibitory), rise in blood pressure, quickening of respiration and vomiting and salivation. In many animals, the reflexes are increased when the cord is separated from the medulla, indicating stimulation of the **spinal centres**.

In an unanaesthetised animal, only the above toxic effects are produced but in a case of central depression as from high doses of barbiturates when the patient is comatose with feeble pulse and respiration, picrotoxin acts as a powerful **analeptic** reinstating normal respiration and greatly lessening the degree of coma. Marshall (1937) found that a convulsive dose is a satisfactory antidote to the depressant action of chlorbutol, paraldehyde, avertin and barbiturates poisoning although such a dose would cause fatality to a normal animal.

For therapeutic use in narcotic poisoning, 1 to 3 mg. is given intravenously or 3 to 6 mg. intramuscularly every fifteen minutes. For continuous administration, 0.1% solution in normal saline is given : 1 ml. containing 1 mg. every minute till the desired therapeutic effect is produced : the first sign of improvement is the restoration of corneal reflex : the respiration improves in rate and depth, blood pressure goes up and coma disappears. It will appear that a comatose patient can tolerate an enormous dose of the poison and even 200 to 300 mg. may be given in 24 to 48 hours. This may be due to rapid detoxification of the drug in circulation in such a condition.

It is of no value in *alcohol* poisoning. *Morphine* acts on the spinal cord and picrotoxin also has action on the same place : the two combined tend to increase convulsion and therefore picrotoxin is not suitable in morphine poisoning.

Picrotoxin is occasionally given orally for in night sweats³⁹².

AVAILABLE as 3 mg. ampoules.

SUMMARY.—With therapeutic doses, picrotoxin stimulates the respiratory centre but its main use is as **antidote to coma** of narcotic poisoning and given in a frequently repeated dose intravenously that can cause convulsion in a normal person. Orally, it is sometimes used for night sweats.

(392) R

Picrotoxin gr. 1/60

Atrop. Sulph. gr. 1/120

Agaracin gr. 1/12

Ext. Gent. q.s.

Pil : at bed time for night sweat.

2. NIKETHAMIDUM (*Nikethamid.*), $C_{10}H_{14}ON_2$

Nikethamide, popularly called *Coramine*, is dimethylamine of pyridine-beta-carboxylic acid, prepared by interaction of thionyl chloride on nicotinic acid and final treatment with diethylamine: contains not less than 98% of $C_{10}H_{14}ON_2$.

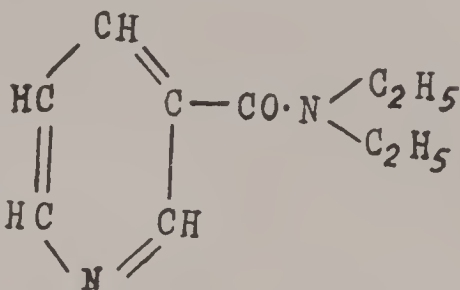
A colourless or yellowish oily liquid or crystalline solid, inodorous and with a slight bitter taste followed by a feeling of slight warmth.

Miscible easily in water, alcohol (90%), ether, chloroform and benzene. A solution for injection is sterilised by autoclaving or by filtration.

Dose, 5 to 15 grains or 0.3 to 1 gramme; subcutaneous, intramuscular and intravenous injections, 4 to 15 grains or 0.25 to 1 gramme.

Injectio Nikethamidi (*Inf. Nikethamid.*), See p. 45. Strength is 0.25 gramme in 1 ml. (25%).

Dose, subcutaneously, intramuscularly or intravenously, 15 to 60 minims or 1 to 4 ml. Contains in 4 ml. 1 grm. and in 60 min., 15 grs.



Pharmacology [and Therapeutics]

Nikethamide has action like leptazol on the *medullary centres* raising the respiratory rate and depth and the blood pressure. The carotid sinus reflex becomes more active and the stroke volume of the heart increased, the venous pressure remains

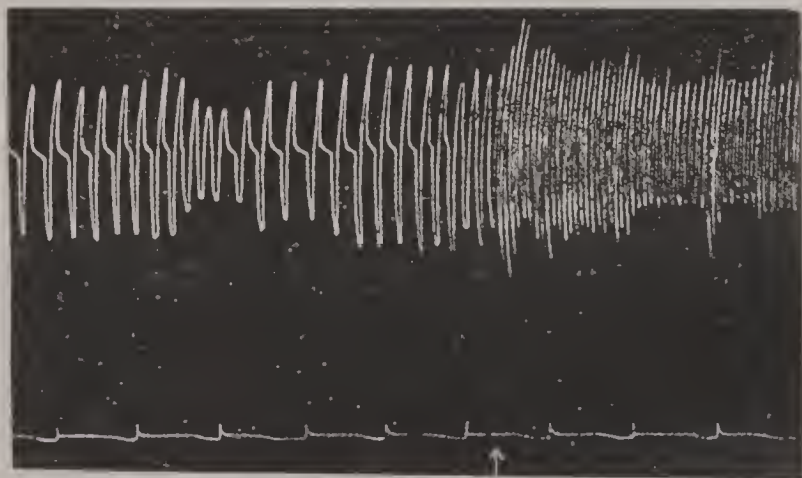


Fig. 34.—Effect of Coramine on Respiration on a morphinised rabbit: Respiration, slowed by morphine, is markedly quickened. (Ciba)

unaltered: coronary circulation is unaffected or slightly increased. In bigger dose, it causes excitement and tremors and if this is more increased, convulsion. It has consequently been frequently used as a respiratory and cardiac stimulant in various conditions in which these are depressed.

It may be used as “awakening agent” in deep narcosis especially of morphine, avertin and of barbiturates. It is also used in schizophrenia.

In such cases a slow intravenous injection of 5, 10 or 15 ml. followed by similar doses intramuscularly may tide over the crisis. One method is to give 5 c.c. every 5 minutes for an hour and then to repeat hourly till the reflexes return and spontaneous movements appear. Picrotoxin 3 mg. every 15 minutes may be alternated with nikethamide.

A case of morphine poisoning by 1.5 g. had 42.5 c.c. intravenously in 15 minutes followed by a similar dose in the next 5 hours, total of 85 c.c. and had recovery.

Nikethamide (*Coramine*) has low toxicity, the lethal dose in a rabbit is 12,000 mg./kg. and the increase in the blood pressure is obtained with 5 mg./kg. and respiratory stimulation with 10 to 20 mg./kg. The therapeutic margin is thus very wide.

The drug is easily destroyed in the system without any accumulation or increased tolerance.

Although the comparative merits of this and of leptazol are not yet fully worked out, probably leptazol action is more quick and lasting. These have largely replaced camphor as analeptic and may be combined with strychnine or ephedrine.

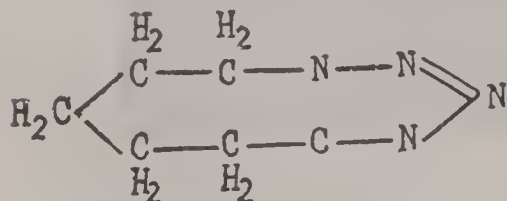
CORAMINE-ADINOSINE, *Liquid* oral or ampoule (in 1 c.c. 0.2 g. theophylline and 0.001 g. adenosine) and *tablet* (coramine and calcium thiocyanate 0.325 g., theophylline 0.075 g. and adenosine 0.001 g.) used in coronary insufficiency and hypertension.

CORAMINE-CAFFEINE, *Liquid* oral or ampoule (in 1 c.c. 0.1 g. coramine, 0.1 g. caff. sod. salicyl. and 0.00025 g. strychnine) and *tablet* (0.2 g. coramine calcium thiocyanide, 0.05 g. caffeine and 0.00025 g. strychnine) used in physical and mental exhaustion, collapse, fainting fits and in air sickness. CORAMINE-EPHEDRINE, tablet, liquid and ampoule are available for bronchial asthma.

CYCLITON (Not official) is diethylamide-dimethyl isoxazol carboxylic acid and has a similar action as analeptic orally 0.1 gm. or parenterally 2.2 c.c. (in ampoule).

3. LEPTAZOLUM (*Leptazol.*), $C_6H_{10}N_4$

LEPTAZOL popularly called *Cardiazol* also *Metrazol* is pentamethylene tetrazole $CH_2.(CH_2)_4.C.N.N:N.N$ and may be prepared by the interaction in cold benzene solution of hydrazoic acid and cyclohexanone.



Colourless crystals or white crystalline powder, inodorous with slightly pungent taste: readily soluble in water, alcohol 95%, solvent ether and in chloroform.

Dose, $\frac{3}{4}$ to $1\frac{1}{2}$ grains or 50 to 100 mg

Injectio Leptazoli (*Inj. Leptazol.*), See p. 44. (Strength 10%).

Dose, 8 to 15 minims or 0.5 to 1 ml. by subcutaneous injection. One ml. (15 min.) has 100 mg. ($1\frac{1}{2}$ gr.).

Pharmacology [and Therapeutics]

Popularity of camphor as an *analeptic* (or restorative) in the continent of Europe led to researches to prepare it and allied compounds synthetically especially one soluble in water. One

such successful compound is leptazol. It is readily absorbed and is **stimulant** to the **vaso-motor** and the **respiratory centres** of the *medulla*, increasing the respiratory movements, raising the blood pressure also the heart rate and consequently found useful when these are depressed as in lobar pneumonia and chloroform and other narcotic poisoning and administered both orally and hypodermically. No direct action on the heart muscles or the blood vessels has yet been proved.

It stimulates the **higher centres** of the brain and in 3 c.c. dose, given slowly intravenously it has an **awakening effect** in profound narcosis [and is occasionally used to counteract the effects of an overdose of an anæsthetic especially of barbiturates : frequent intravenous injections of 5 ml. are necessary till any response is obtained]. With even higher dose, it is a **convulsant** [and is used for treatment of schizophrenia in 5 to 7 c.c. dose quickly intravenously : short epileptiform convulsion follows and with intervals of 3 to 4 days about 15 injections are given. The disturbance caused in the brain-stem probably reactivates the dormant nervous function].

SUMMARY.—*Nikethamide* and *Leptazol* are powerful stimulants to the respiratory and vasomotor centres in the *medulla* : used in cardio-respiratory failure especially of profound narcosis of anæsthetics when frequently repeated doses intramuscularly or intravenously are indicated.

4. OXYGENIUM

Oxygen is prepared by the fractional distillation of liquid air or by the electrolysis of water : it must contain not less than 98% by volume of Oxygen. It is a colourless, inodorous, tasteless gas, compressed and supplied in metal cylinders.

Pharmacology [and Therapeutics]

The normal blood of a human being contains about 18·5% of oxygen as oxy-hæmoglobin in red blood corpuscles and about 0·3% of it is dissolved in the plasma. The inspired air contains 20·9%. As in health the red cells are already 95% saturated, by increasing the oxygen pressure in the inhaled air, the oxygen content of hæmoglobin cannot be much increased but that of the plasma can, to nearly 2·2%.

In the normal process of oxidation, the plasma oxygen is used first and the combined oxygen after. In a case of anoxæmia, therefore, if oxygen is given by inhalation at a higher pressure, the tissue oxidation is carried on from the oxygen dissolved in the plasma and this supplements the oxygen combined with the red blood cells.

All bodily activities especially of the muscle tissues, are dependant on the adequate supply of oxygen. When this is deficient, as in various diseased conditions, it is the usual practice to supply oxygen by raising the oxygen-pressure of the inhaled air.

The signs of oxygen deficiency are cyanosis, increased respiratory and pulse rate, fall in blood pressure and increasing depression of the central nervous system.

[Inhalation of oxygen is of undoubted value in many condition of anoxæmia (or anoxia) as in extensive pulmonary consolidation or œdema, collapse of the lungs or in laryngeal and bronchial obstruction: decompensated heart disease, profuse hæmorrhage or severe anæmia: ascent to a high altitude where the oxygen pressure is low: carbon monoxide, nitrite or benzene poisoning: it is also used in nitrous oxide anæsthesia].

The gas as it comes out, is rather cold. It is of advantage to allow it to bubble through warm water. The administration should be nearly continuous and fairly brisk to sufficiently raise oxygen pressure in the alveoli. Considerable quantity is thus required before a sufficient effect is produced. Further, the administration should be started before there is much cyanosis. Lowering of oxygen concentration of the arterial blood to 80 to 85% causes visible cyanosis and consequently damages to the central nervous system and the myocardium: this increases the heart rate and temporarily the force also which is soon followed by depression. Unless this can be prevented by early administration of oxygen, the damage may be too irreparable. The subcutaneous injection has not been proved to be of any substantial value.

MODE OF ADMINISTRATION.—Oxygen is administered by nasal catheters passed up to the posterior nares but better still by B.L.B. mask, from a steel cylinder in a rather rapid continuous stream so that about 2 litres per minute may be given but oxygen is wasted during the expiratory phase. The fastest rate as may be counted during bubbling through water gives only $\frac{1}{4}$ liter per minute which does not very much increase oxygen level in the alveolar air. So if possible, the patient should be placed in a specially made room containing about 50% of oxygen. Administration with a funnel held near the mouth is wasteful and useless as it fails to cause any reasonable oxygen concentration in the alveolar air. Care should be taken not to bring an open flame near it.

An ideal method would be to have an apparatus which would allow oxygen to come out only during inspiration and there should be an outlet for the expired air to pass out.

A prolonged administration in a concentrated form may cause irritation of the epithelia of the respiratory tract.

HELIUM is a light gas and 80% of it with 20% of oxygen may be used and being lighter than air is breathed more easily with less effort: specially suitable for obstruction to air passages, status asthmaticus and caisson disease.

SUMMARY.—Oxygen inhalation in slowly increasing concentration through a nasal catheter, B.L.B. mask or oxygen tent is essential in impending hypoxæmia: the high pressure solution of oxygen in the blood plasma compensates the deficiency.

5. CARBONEI DIOXIDUM, (*Carbon. Diox.*), Carbon Dioxide, CO₂

Prepared from mineral carbonates or from fermentation of sugars. It is a heavy colourless gas and an aqueous solution of it gives a faintly acid taste. Contains not less than 99% v/v of CO₂. It is available, compressed in metal cylinders.

Pharmacology [and Therapeutics]

LOCAL APPLICATION of the gas or a solution of it causes some **irritation** and reddening of the skin and the mucous membrane followed by slight numbness and **local anæsthesia**. [Carbonated baths are sometimes given in arthritis and other chronic diseases. Compressed CO₂ supplied in cylinders, coming out in a fine jet also makes a semi-solid substance called "carbon dioxide snow". This has the temperature of -65°C. to -79°C. and is a caustic, being used for cauterising superficial skin lesions.

INTERNAL ADMINISTRATION.—Carbonic acid in effervescent mixture, is given by the mouth : by causing a mild irritation to the stomach and the intestine, increases the secretions and motility : it is thus a **stomachic** and **carminative**. It causes slight local anæsthesia and acts as **gastric sedative** for vomiting and is also helpful in some cases as a **mild laxative**³⁹³. Soda (aerated) water and lemonade are very favourite drinks : when a large quantity is taken, a large part of CO₂ is belched out but some rapidly makes its way through the walls of the stomach into the blood, and that at the same time accelerates the absorption of other substances present in the alimentary canal. This increases the appetite and gives a general feeling of well-being. Absorbed CO₂ has no systemic action.

Many purgative salts are made in such a way that in contact with water, CO₂ is liberated. This helps in disguising the taste of the salts and also speeds up their laxative action^{394, 395}.

As an aerated water is quickly absorbed into the systemic circulation, the aerated drinks act as better **diuretic** than plain water.

(393) R

Sodium bicarbonate 5, tartaric and citric acids 2 and 1 and sugar 2 are fused together and granulated, This resembles. *Eno's Fruit Salt*. Dose one dessert-spoonful in a tumbler of water. A favourite laxative.

(394) R

(1) Acid. Tartaric. gr. 20
Syrup. min. 90
Aq. ad. ½ fl. oz.

(2) Sod. Bicarb. gr. 40
Sod. Sulph. gr. 30
Aq. ad. fl. oz. 1

(1) and (2) to be mixed and taken while effervescing.

(395) R

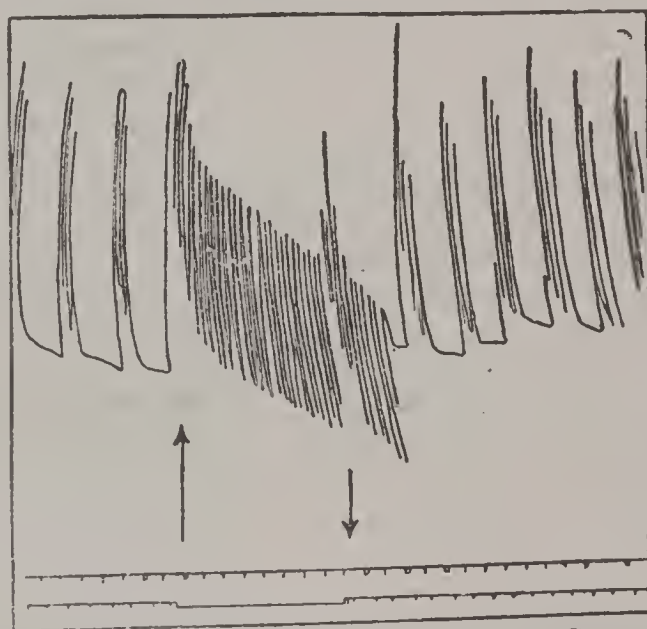
Sod. Sulph. Exsic.
Sod. Bicarb. aa. 5
Acid. Cit.

Acid. Tart. aa. 2½

Granulate : Dose, 1 to 4 tea-spoonful in a tumbler of water.

SYSTEMIC ACTION.—The atmospheric air has 0.4% of CO_2 : being inhaled in a much higher concentration than this it acts as a powerful **respiratory stimulant** increasing both the rate and depth. The action is either specific on the respiratory centre or more probably this is by increasing the acidity of blood flowing through the centre and the carotid body. A 2% concentration of it, increases the volume of exhaled air by 50% : a 3% by 100% and 5% of it by 500%. There is marked increase of respiratory efforts, both in amplitude and frequency especially with more concentrated mixtures. If continued longer, dyspnoea is more marked and the blood pressure moderately rises. If persisted still longer, especially in high concentration, the skin becomes cyanotic and afterwards all stimulating phenomena pass into **depression**. The heart rate is lessened causing heart block.

All these are due to the stimulation of the medullary centres, first the respiratory and then the vaso-motor, ultimately followed by their paralysis. The blood containing the extra CO_2 circulating through the carotid sinus reinforces the increased respiratory activity. But if the centre is profoundly depressed as from narcotic poisoning, the effects are comparatively poor.



(Cushny)

Fig. 35.—Periodic breathing in a rabbit : between the arrows, 6% of CO_2 in air was given by inhalation. The respiration immediately became quick and regular but relapsed again to the former condition on stopping it.

CIRCULATION.— CO_2 causing alteration of pH of the tissue (acidosis) has a peripheral action also, local vaso-dilatation. If the gas is given by inhalation, it is carried to the brain in higher concentration : the effect is stimulation of vaso-motor centre and peripheral vaso-constriction with a rise of systemic

blood pressure. The cerebral blood vessels however are dilated : this is helpful in increasing the blood supply to the vital centres. (Gibbs and Lannox, 1936). It is also claimed that the tone of skeletal muscles is increased : this favours venous return to the heart (Henderson, 1936). Myocardium is made more distensile with increased cardiac filling and output. But the conduction of cardiac impulse is somewhat depressed. Severe acidosis however may cause complete heart block. [In asphyxia as of drowning or in narcotic poisoning, 5% of CO₂ with 95% of O₂, called *Carbogen*, or in even more concentrated form as 7% (Henderson and Haggard, 1930), is given for stimulating the respiratory centre. Given for 5 to 10 minutes during recovery from a volatile anæsthetic, the respiratory movements are increased, the bronchioles are cleared of mucus, post-operative collapse of the lung is prevented and the anæsthetic is excreted more quickly. Such a combination has also been found an useful expectorant is clearing the lungs of a mucopurulent exudate : some types of Cheyne-Stokes breathing may be changed to normal regular breathing].

CARBON MONOXIDE, CO is only of toxicological interest. A concentration of 0.1% in air is dangerous. The symptoms are anoxia, tachypnœa, headache, giddiness, prostration and ultimately coma, stoppage of respiration and death. Carbon monoxide combines with hæmoglobin to form carboxyhæmoglobin which stops oxygen transport.

Treatment is inhalation of oxygen-carbon dioxide mixture.

D. Drugs Acting on the Spinal Cord

1. The effects of excitation or depression are best shown on the *anterior horn cells*. This **excitation**, direct or referred, is evidenced by increased muscular activity and in toxic doses, by convulsions. The spinal convulsions differ from cerebral in being widespread, symmetrical and tonic, but the cerebral is more clonic and localised or irregular. **Convulsant drugs** in the *spinal group* are Strychnine, Brucine, Caffeine, Thebaine, Sparteine, and Ammonia (given intravenously) : in the *cerebral group*, Atropine, Cocaine, Leptazol, Nikethamide, Essential oils and Santonin.

Drugs that **depress** the activity of the anterior horn cells are,

- (i) Narcotics, as Alcohols, Chloroform, Ether, Cannabis indica and Opium : basal anæsthetics : Mephencsin (myanesin).
- (ii) Bromides : Magnesium salts when given parenterally.
- (iii) Gelsemium and to a less extent Physostigmine, Lupulin and Calcium.
- (iv) More rarely, salts of heavy metals as Antimony, Zinc and Silver salts.

2. The most important drug acting on the *posterior portion* of the spinal cord, increasing the receptivity of the afferent neurones and also of the reflex arc, is Strychnine.

NUX VOMICA (*Nux Vom.*), *Strychni semen*, *Kuchila*

Nux vomica is the dried ripe seed of *Strychnos Nux-vomica*. It is disc-shaped, sometimes irregularly bent, 0·4 to 1 inch (10 to 30 mm.) in diameter and 0·1 to 0·18 inch (4 to 6 mm.) in thickness and slightly concavo-convex with rounded or somewhat acute margins and of ash-grey colour. It is covered with silky hair. It has no smell but an extremely bitter taste.

It grows in Orissa, Cochin China and in Ceylon.

The seed contains (i) two alkaloids, *Strychnine* and *Brucine* and the strychnine-yield is standardised to be not less than 1·2%. (ii) *Caffeotannic acid* in combination.

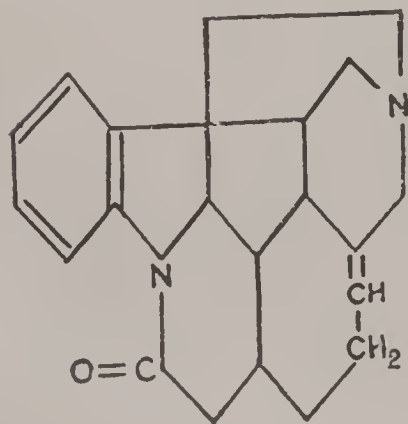
NUCIS VOMICÆ PULVIS (*Nuc. Vom. Pulv.*) : yellowish grey powder of nux-vomica.

OFFICIAL PREPARATIONS.—(i) **Nux Vomica Præparata** (*Nux. Vom. Præp.*), Finely powdered Nux Vomica, adjusted to contain 1·2% of strychnine. In 4 gr. about 1/20 gr. of strychnine. Dose, 1 to 4 grains or 60 to 250 mg. (ii) **Extractum Nucis Vomicæ Liquidum** (*Ext. Nuc. Vom. Liq.*), See p. 40. Contains 1½ gr. of strychnine in 110 min. or 1·5% w/v. Dose, 1 to 3 minims or 0·06 to 0·2 ml. (iii) **Extractum Nucis Vomicæ Siccum** (*Ext. Nuc. Vom. Sicc.*), See p. 39. Dose, ¼ to 1 grain or 5 to 60 mg. (iv) **Tinctura Nucis Vomicæ** (*Tinct. Nuc. Vom.*), See p. 59. About 1/15 gr. of strychnine in 60 min. (0·125%). Dose, 10 to 30 minims or 0·6 to 2 ml.

STRYCHNINA, Strychnine, $C_{21}H_{22}N_2O_2$, (Not official).—It occurs in colourless, inodorous, trimetric prisms which are intensely bitter in minutest dilution and very feebly soluble in water.

INCOMPATIBLES.—Alkalies, iodides and bromides.

STRYCHNINÆ HYDROCHLORIDUM (*Strych. Hydrochlor.*), Strychnine Hydrochloride, $C_{21}H_{22}O_2N_2 \cdot HCl, 2H_2O$.



Strychnine

It is the hydrochloride of the alkaloid strychnine, obtained from nux vomica seeds. It contains between 82 to 84% of strychnine. Colourless trimetric prisms, with intensely bitter taste: soluble at 15·5° in 40 of water and about in 80 of alcohol (90%).

Dose, 1/30 to ½ grain or 2 to 3 mg.

OFFICIAL PREPARATIONS.—(i) **Liquor Strychninæ Hydrochloridi** (*Liq. Strych. Hydrochlor.*). See p. 50. Strength 0·82% of strychnine. Dose, 3 to 12 minims or 0·2 to 0·8 ml. (ii) **Injectio Strychninæ Hydrochloridi** (*Inj. Strych. Hydrochlor.*), See p. 47. Dose, 1/30 to 1/16 gr. or 2 to 4 mg. The injection, if not otherwise stated, will be dispensed containing 1/16 gr. in 15 min. or 4 mg. in 1 ml.

Pharmacology [and Therapeutics]

The pharmacological actions of nux vomica are due to its chief active principle, strychnine.

Strychnine was first introduced in Medicine in 1540 but was not largely used until about two hundred years after. For many years, it was frequently used as general tonic and considered to be a cardio-respiratory stimulant of great value but is now falling into the back ground. It is however of some value in narcotic poisoning as a *respiratory stimulant*.

APPLIED EXTERNALLY, Strychnine is a powerful protoplasmic poison and brucine is a feeble anæsthetic but these are too toxic to be of any practical use.

TAKEN BY THE MOUTH, strychnine is intensely bitter and increases the **salivary secretion** and also reflexly, the appetite and the gastric secretion. It is therefore **stomachic** and **digestive**. [On account of slower absorption and sustained local action, the tincture or the extract of nux vomica is more commonly used than strychnine itself].

ABSORPTION AND ELIMINATION.—It is slightly absorbed from the stomach and more so from the intestine. About 10 to 20% of it is slowly excreted in the urine and the rest is oxidised in the liver. No obvious tolerance develops in most cases.

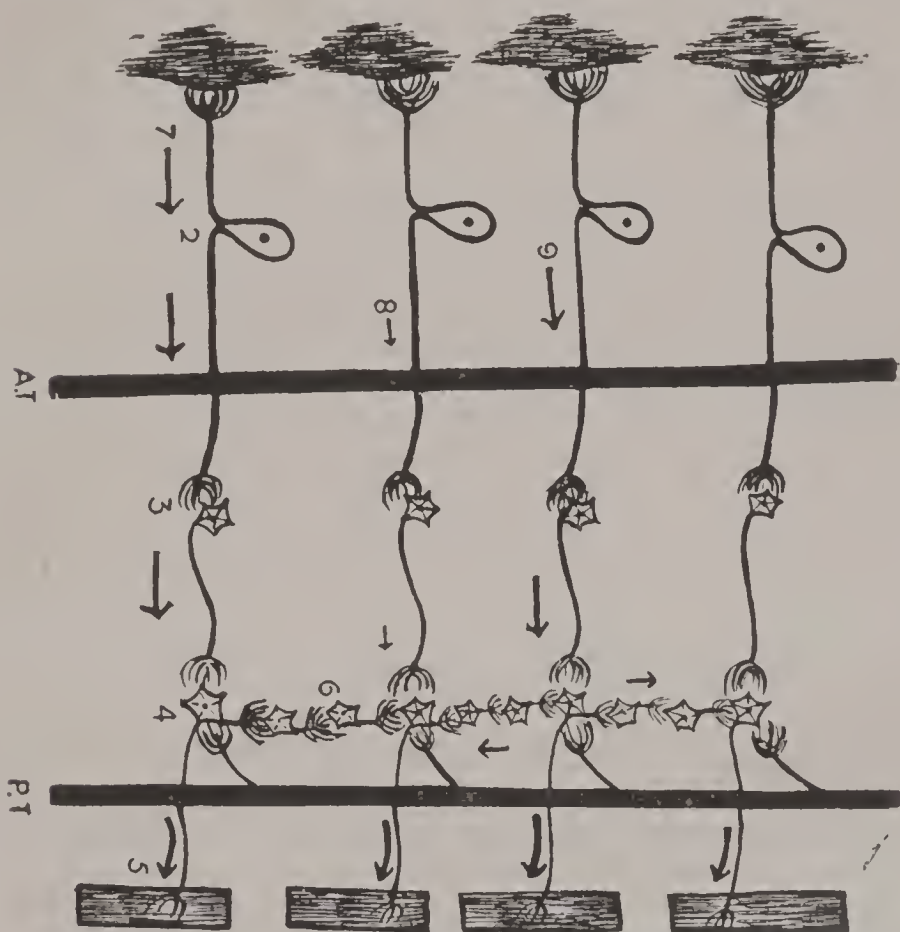


Fig. 36.—(1) Skin. (2) Posterior root ganglia. (3) Posterior horn cells. (4) Anterior horn cells. (5) Skeletal muscle. (6) Intersegmental nerve cells and fibres. (7) Minimal cutaneous stimulus capable of causing muscular contraction in a normal animal. (8) Subminimal stimulus made effective by strychnine. (9) Minimal stimulus causing widespread muscular contraction. (The last two are manifested in a strychninised animal only).
AT, afferent tract : PT, pyramidal tract.

(i) Absorbed into the circulation, in **toxic doses** (as $\frac{1}{2}$ to 2 grains), strychnine produces its **specific poisonous action** on the

nervous system. The most striking effect is manifested on the **SPINAL CORD**.

Normally, the afferent impulses that travel up the sensory nerve endings into the spinal cord regulate the motor movements and reflex functions. The effects produced are in proportion to the strength of the stimulus applied and an impulse of moderate intensity causes the contraction of a localised group of muscles only with relaxation of the antagonists. Strychnine **increases the receptivity of the sensory system, lessens the resistance** to the passage of impulse through the spinal cord and exaggerates the **reflex functions**. The result is that the threshold of response to stimuli is lowered and a minimal stimulus, which in a normal person would hardly cause any motor activity, causes marked muscular movements. This is a strong but co-ordinated purposive single reflex. But if a stronger and more sudden shock is applied, all the muscles contract together without any inhibition of the antagonists (Cushny). The whole body is contracted and becomes stiff. This is maximal and any stimulus of higher intensity does not cause a greater effect. Muscular contraction and convulsion that appear, are always the effect of some kind of afferent stimulus and never spontaneous.

That the convulsions are spinal in origin are demonstrated by giving strychnine to an animal after destroying the brain or severing the spinal cord below the medulla: convulsions still follow.

Probably the *anterior horn* and the *posterior root ganglia* are the sites of this hyperexcitability (Barenne 1939) and not the synapses of the neurones between the posterior roots and the nerve cells of the anterior horn as was formerly believed. Three mechanisms act: (a) lowering the threshold of excitability, (b) preventing the loss of excitability from continuous stimulation and (c) increasing the duration of the hyperexcitable phase (Heinbecker and Bartley, 1939).

The signs of poisoning in an animal are manifested as considerable exaggeration of reflexes so that even a slight noise leads to violent movements. In the beginning, a certain amount of restlessness with occasional involuntary twitchings of the muscles are seen. The slightest stimulus causes contraction of a small group of muscles. With a more powerful one, all the muscles of the body are affected causing convulsion. The extensor muscles being more powerful than the flexors, the head is thrown back, the fore and hind limbs are extended and the trunk is arched backward. The respiration is temporarily arrested resulting in asphyxia and cyanosis. After a variable period of stiffness, which may be 20 to 60 seconds, a certain amount of relaxation occurs so that the tonic or the state of complete stiffness is succeeded by clonic or irregular movements, till the relaxation is complete. This is followed by a period of diminished reflex function from exhaustion. Soon after, more

convulsive attacks follow even without an apparent stimulus which finally result in considerable exhaustion, general depression and death.

After prolonged administration, this initial increase of the functional activity of the spinal cord is followed by depression. The sensory portion is affected before the motor so that after sometime, a stimulus, direct or reflex, fails to cause any response.

(ii) Given in **therapeutic doses**, to a human being, strychnine increases the receptivity of the reflex arc and facilitate to some extent the normal bodily functions.

HIGHER CENTRES.—There is a decidedly increased activity of the **sense organs**. The sense of smell becomes more acute and that of touch more delicate. Hearing and sight also become more acute and the field of vision is enlarged : the last is due to direct action on the retina. Even painful stimuli are more acutely perceived. [Strychnine is therefore used in toxic amblyopia especially from excessive tobacco smoking and also used as a general nervine tonic³⁹⁶],

CEREBRUM is comparatively little affected. In cases of poisoning, consciousness is maintained till the fatal end. There is no hallucination or delirium.

Strychnine increases the **capacity for muscular work** and lessens fatigue. Further, it stimulates the **activities of a paralysed or weakened muscle group**, striped, unstriped and cardiac.

It increases the activity of the spinal centres of the reproductive organ : it is believed to act as a **mild aphrodisiac** and probably also slightly as an **emmenagogue**.

MEDULLA.—This is also similarly affected so that the usual afferent stimulus produces exaggerated effects. The **respiratory movements** become quicker and deeper. Strychnine is prescribed to stimulate the respiratory centre in narcotic poisoning³⁹⁷⁻³⁹⁸ or in pneumonia and also to increase the reflex excitability of the **bronchial muscles** to expel secretions collected inside the tubes].

With a therapeutic dose, the **vaso-motor centre** is moderately stimulated and the blood vessels are constricted and the blood pressure is slightly raised. The **vagal centre** is also slightly stimulated and the heart beats tend to be slower than normal. The strength of the contractions is somewhat increased, probably due to slight direct action on the **heart muscles**. [For all these

(396) R
Tinct. Nuc. Vom. min. 10
Ext. Damian. Liq. min. 30
Ferr. Pyrophosph. gr. 2
Glycer. min. 80
Aq. Menth. Pip. ad. fl. oz. 1
A nerve tonic.

Atrop. Sulph. gr. 1/60
Aq. pro Inj. min. 15
Hypodermically.

(398) R
Strych. Hydrochlor.
g. 1/50 to 1/20
Aq. pro Inj. min. 15
Hypodermically.

(397) R
Strych. Hydrochlor. gr. 1/30

combined, strychnine with a therapeutic dose, often improves the general circulation and is prescribed in impending heart failure but should be given hypodermically].

The *vaso-constricting* effect is more marked on the blood vessels inside the abdomen. The skin and other superficial vessels are not constricted : these may rather dilate : this is due to stimulation of the *vaso-dilator centre*. Thus blood is diverted from the abdominal viscera to the skin, muscles, heart, lungs and the brain.

During convulsion, the blood-pressure is raised but it falls soon after, during relaxation. Strychnine stimulates the suprarenal secretion. This probably augments the circulatory effects.

PERIPHERAL NERVES.—In contrast to the central action, direct application of strychnine to a motor nerve trunk **diminishes its excitability**. The motor nerve endings are paralysed by large doses, but the central action is so predominant that paralysis is not at all manifested.

AUTONOMIC NERVOUS SYSTEM.—By slightly **augmenting the reflex functions**, the force of contraction and tonicity of the unstriated muscles are slightly increased. The gastric tone is improved^{399, 400} increasing the appetite, and the peristaltic movements of the intestine are accelerated ; [It is therefore a **stomachic** and a helpful adjunct to purgatives⁴⁰¹, especially for chronic constipation. Atony of the bladder causing **retention of urine**, is occasionally treated by strychnine (gr. 1/50 or more hypodermically)].

VOLUNTARY MUSCLES.—In some cases a small therapeutic dose of strychnine tends to increase the muscular tone : this action is probably secondary to spinal cord effects.

METABOLISM.—On account of excessive muscular activity, more O₂ is absorbed and CO₂ liberated, blood sugar rises and glycogen disappears from the liver and the muscles. As increased heat production is associated with increased loss of heat also through the skin, the surface temperature does not appreciably alter.

SUMMARY.—The *systemic action* of strychnine is to increase the **receptivity of the reflex arc** stimulating the sensory functions and vasomotor and respiratory centres in the medulla : increasing the activities of muscles, stripped, unstriated and cardiac also general metabolism : *locally*, it is a **bitter-stomachic** on the alimentary canal. The *toxic action* is to enormously increase the **motor reflex functions** a moderate stimulus causing spinal type of convulsions.

(399) R
Acid. Hydrochlor. Dil. min. 10
Tinct. Nuc. Vom. min. 10
Tinct. Cardam. Co. min. 20
Aq. Chlorof. ad. fl. oz. 1
Half an hour after food for
atonic dyspepsia.
(400) R
Sod. Bicarb. gr. 15
Tinct. Nuc. Vom. min. 10

Sp. Chlorof. min. 20
Inf. Gent. Co. Rec. ad. fl. oz. 1
Half an hour before food.
(401) R
Aloin gr. ½
Ext. Nuc. Vom. Sicc. gr. ½
Ext. Bellad. Sicc. gr. ½
Pulverat. Ipecac. gr. ½
Glycer. Trag. q.s.
A dinner pill.

Brucine, the other alkaloid, somewhat resembles strychnine in action but is much weaker, requiring 30 to 40 times a dose to cause a similar effect. But such doses paralyse the motor nerve endings in the voluntary muscles, more marked in frogs. So it is not used therapeutically.

DRUGS ACTING ON THE MOTOR SYSTEM (Not official).

1. **MEPHENESIN**, Dihydroxy-(2-methyl phenoxy) propane acts on the *motor system of brain stem and spinal cord* causing depression of inter-neuronal conduction and acts as a muscle relaxant in **surgical operation** as auxiliary to a general anæsthetic or in **tetanus** and **strychnine poisoning**, slowly intravenously in 5 to 10 ml. dose : effects are produced in 1 to 2 minutes and lasts for 20 to 30 minutes, may be kept up by intramuscular injections. The action is sometimes uncertain and venous thrombosis may result. The curare preparations are probably more efficient and safer. In **spastic and hyperkinetic states**, and in certain **psychosis**, oral administration of 0.5 to 1 g. one to six times daily may be given as necessary.

Available as **MYANESIN** or *Tolserol* ampoules (10%) 10 ml. each and **MYANESIN ELIXIR** (oral) 15 ml. ($\frac{1}{2}$ ounce) containing 1 g.

2. **PARFANIT**, diethylaminoethylester of phenyl cyclopentane carboxylic acid, has been used in **Parkinsonism** : suggested doses are 12.5 mg. every 3 hours on the 1st, 12.5 mg. and 25 mg. alternately every 3 hours on the 2nd and 25 mg. every 3 hours on the 3rd day and slowly increased. A smaller dose scheme is 6 of 6.25 mg. tablets on the first day : one tablet added daily to make 12 tablets on the 7th day : then increased by 2 tablets a day to 22 tablets on the 12th day : then 50 mg. tablets are started one 3 times daily slowly reaching 400 mg. daily. The full average dose is 200 to 400 mg. daily. Improvement may follow in 15 to 30 days. *Side effects* are giddiness, weakness, dry mouth and blurred vision and when these appear, dose should be reduced.

Available is 6.25 mg. and 50 mg. tablets.

3. **ARTANE**, trihexyphenidyl, 1 mg. twice daily slowly increased, has been found useful in arterio-sclerotic type of Parkinsonism.

(These may be combined with *belladonna* and *amphetamine*).

E. Drugs Acting on the Peripheral Nerves

1. MOTOR NERVE ENDINGS

CURARE (Not official)

This is the arrow poison of the South Americans, prepared from the bark of *Strychnos Toxicifera* and other varieties of *Strychnos*.

The active principle of curare is *d*-tubocurarine, $C_{38}H_{44}O_6N_2$. The other principles are curine, $C_{36}H_{38}O_6N_2$ and proto-curarine, $C_{19}H_{23}O_2N$ but of less importance.

The arrow poison taken by the mouth has practically no action as the absorption is slow and elimination by the kidneys is rapid. But it is more readily absorbed from a wound surface or from hypodermic injection and produces its specific *blocking effect* on the *motor myoneural junction*, causing **paralysis of voluntary muscles**. The nerve fibres are unaffected.

The action starts in the muscles supplied by the cranial nerves, limb muscles, abdominal muscles, intercostals and finally in the diaphragm. The muscles are paralysed one after

the other but slow, weak and somewhat jerky respiratory movements continue for sometime. Afterwards these also fail, asphyxia appears but no convulsion as the muscles are already paralysed. The heart fails and the fatal end follows. The effect of a moderate therapeutic dose is short-staying owing to its rapid elimination. It is thus a **safe muscle relaxant**.

In experimental intravenous injection of *d*-tubocurarine, in a normal person the following effects were found which clearly indicate the mode of action. (a) 1 to 2 mg. caused diplopia only from external ophthalmoplegia : (b) 10 mg. caused diplopia, ptosis, squint, a feeling of weakness and partial paralysis of other muscles : (c) 20 mg. caused the above effects in one minute and paralysis of facial and neck muscles in 2 minutes with rapid spread to larynx, limbs, abdomen and intercostals : tidal air fell from 750 to 500 ml. but no change in respiratory rate. Recovery began in 15 minutes in the reverse order but the eye paralysis disappeared in 3 to 4 hours. (d) 30 mg. caused complete paralysis including the intercostals in 3 minutes. At 5 minutes, the tidal air fell from 750 to 115 ml. (diaphragmatic paralysis) and artificial respiration was given : muscular power was restored in 30 to 40 minutes but eye signs persisted for 4 hours. (Prescott, 1946).

It has been found that acetyl choline, prostigmin and neostigmine also potassium chloride are decurarizing agents : given in adequate dose, these can remove the curare nerve-muscles block. So probably curare acts by preventing either acetyl choline production or its normal utilisation. The anti-curare action of potassium ion is more temporary (p. 247, 252).

UNSTRIPED MUSCLES are not affected with a small dose. The autonomic sympathetic **GANGLIA** are paralysed by large doses. Stimulation of the vagus does not slow the heart. The **SENSORY NERVE ENDINGS** are not affected. The **CENTRAL NERVOUS SYSTEM** is *unaffected* unless the poison is directly applied when it may cause convulsion of picrotoxin type.

METABOLISM is slightly lowered : this is more from diminution of movements caused by muscular paralysis. It may cause salivation.

Given by intramuscular or subcutaneous injection, *d*-tubocurarine may cause some *histamine effect* but this is absent in intravenous injection.

FATE OF CURARINE.—About 30 to 40% is excreted in the urine (Mahfouz, 1949) but it is extensively destroyed by all tissues throughout the body and this destruction is not wholly dependent on the liver or the kidneys (Everett, 1948).

THERAPEUTIC USES.—(i) Curare has recently been used to increase muscular relaxation in anæsthesia so as to lessen the quantity of the anæsthetic and intensity of anæsthesia and yet have all the advantages of full surgical relaxation. The anæsthesia of the 1st and 2nd plane is obtained : this will not fully abolish the reflexes of the upper abdomen and without going any further, curarine may bring in the necessary effect and this is not harmful on the circulation and the respiration.

As sometimes *hypersensitivity* is present, a test dose of 5 mg. of *d*-tubocurarine is given. If the effects are normal, 2 minutes after 10 mg. is given and immediately after 0.5 g. of thiopentone (separately). The anaesthesia is maintained by 50% $N_2O + O_2$ + thiopentone and a further injection of 5 mg. of *d*-tubocurarine is given if required. A post-operative injection of neostigmine and atropine is helpful. Cyclopropane may also be used instead of thiopentone.

(ii) In certain **neurological conditions** when more prolonged action is necessary, oily injection is indicated: for a symptomatic relief of hypertonia, tremors and inco-ordination as of infantile spastic paralysis, spasticity from spinal injury or disease and for athetoid state, it is given intramuscularly twice a week in 0.25 mg. per pound body weight doses.

(iii) In **tetanus**, watery solution intravenously causes temporary effects: 2 to 3 c.c. may be given: oily solution, 3.5 mg./kg. of body weight has more sustained effect.

(iv) It is also used for limiting the range of muscular movements of *leptazol convulsion* and as a diagnostic test for *myasthenia gravis* (such persons become hypersensitive).

The overaction as failure of respiration is controlled by intravenous injection of 2 ml. of 1 in 2000 solution of neostigmine, also artificial respiration.

COMMERCIAL PREPARATIONS are INTOCOSTIN one ml. contains 20 mg. or 20 units: *d*-TUBOCURARINE CHLORIDE (B.W.) 1.5 ml. contains 15 mg.

Oily injection of *d*-tubocurarine, (Tubarine) 30 mg. per ml. in rubber capped phial of 20 c.c. is available.

2. SENSORY NERVE ENDINGS

Drugs paralysing the **sensory nerve endings** are of greater importance. These have a large field of usefulness as local anaesthetic and are frequently used. The most important of this group is *cocaine*.

COCAINA (*Cocain.*), Cocaine, $C_{17}H_{21}O_4N$

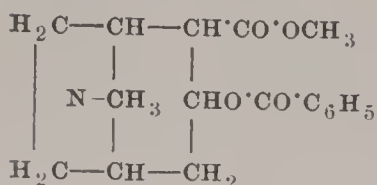
It is an alkaloid obtained from *Erythroxylum Coca* leaves and its varieties, also synthetically from ecgonine, this being methylbenzoylecgonine. This is related to tropine the base of atropine. Coca is indigenous to Peru in South America and has been cultivated in India, Ceylon and in Java.

Colourless, inodorous, monoclinic prisms, with bitter taste followed by tingling and numbness. This was first isolated by Niemann in 1860.

Cocaine is almost insoluble in water. It is soluble at 15.5° in 10 parts of alcohol (90%), in 4 of solvent ether, in 0.5 of chloroform, in 4 of oleic acid, in 24 of olive oil and about in 120 of liquid paraffin; also soluble in 2 of warm anhydrous lanoline and 3 of benzene.

UNGUENTUM COCAINÆ (Not official).—Cocaine 4, oleic acid 16 and lard or suet 80: contains 4% of cocaine.

1. COCAINÆ HYDROCHLORIDUM, (*Cocain. Hydrochlor.*),
 $C_{17}H_{21}O_4N$, HCl.



This is the hydrochloride of the alkaloid, cocaine. A colourless, inodorous crystalline powder with a bitter taste followed by a sensation of tingling and numbness: soluble in 0.5 of water, in 3 of alcohol (90%) and in 3 of glycerin: insoluble in olive oil. The solution keeps better by

adding $\frac{1}{3}\%$ of boric acid to it.

Dose, $\frac{1}{8}$ to $\frac{1}{4}$ grain or 8 to 16 mg.

(i) *Lamellæ Cocainæ* (*Lamell. Cocain.*).—It contains $\frac{1}{50}$ gr. (1.3 mg.) of cocaine hydrochloride and $\frac{1}{20}$ gr. (3.5 mg.) of the basis containing gelatin and glycerin.

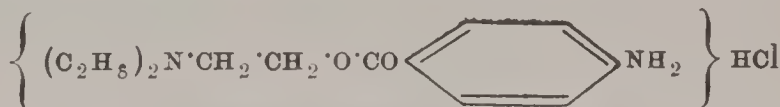
(ii) *Oculentum Cocainæ* (*Oculent. Cocain.*).—Cocaine hydrochloride 0.25 g., yellow paraffin 90 g. and wool fat 10 g. (0.25%).

(iii) *Suppositorium Cocainæ* (*Supp. Cocain.*).—Each contains $\frac{1}{4}$ gr. (15 mg.) of cocaine hydrochloride.

(iv) *Trochiscus Kramerizæ et Cocainæ* (*Troch. Kramer. et Cocain.*).—Each contains $\frac{1}{20}$ gr. of cocaine hydrochloride and 1 gr. of dry extract of krameria, made with sucrose, acacia and tolu.

2. PROCAINÆ HYDROCHLORIDUM, (*Procaïn. Hydrochlor.*),
 NOVOCAINE, Planocaine, Kerocaine, Ethocaine Hydrochloride,
 $C_{13}H_{20}O_2N_2$, HCl.

Procaine is prepared by the interaction of chloroethyldiethylamine and sodium *p*-aminobenzoate. It is a colourless, inodorous, crystalline powder with a slightly bitter taste followed by a temporary anæsthesia of the tongue. Soluble in 1 of water (solution neutral in reaction) and in 8 of alcohol (90%).



OFFICIAL PREPARATIONS.—(i) *Injectio Procaïnæ et Adrenalinæ Fortis* (*Inf. Procaïn. et Adrenal. Fort.*), Procaine hydrochloride 2 g., sodium chloride 0.5 g., chlorocresol 0.1 g., adrenaline hydrochloride solution 2 ml., sodium metabisulphite 0.1 g. and water for injection, to 100 ml. A 2% solution. (ii) *Injectio Procaïnæ et Adrenalinæ Mitis* (*Inf. Procaïn. et Adrenal. Mit.*), Sterile solution of procaine hydrochloride (2%) 25, injection of sodium chloride 75 and injection of adrenaline chloride 0.2 ml. Dose, for infiltration anæsthesia, up to 10.5 fluid ounce or 300 ml.

3. AMETHOCAINÆ HYDROCHLORIDUM (*Amethocain. Hydrochlor.*),
 Tetracaine Hydrochloride, Anethaine, $C_{15}H_{24}O_2N_2$,
 HCl.

This is the hydrochloride of *p*-*n*-butyl-aminobenzoic ester of β -dimethylaminoethanol, prepared by esterifying β -dimethylaminoethanol with *p*-*n*-butylaminobenzoic acid.



It should contain between 98.5 to 101% of $C_{15}H_{24}O_2N_2 \cdot HCl$.

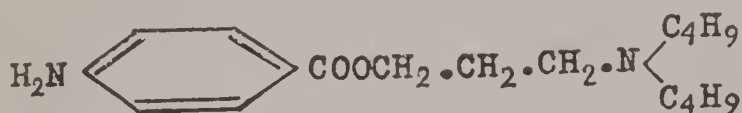
A white crystalline powder, inodorous with a slight bitter taste followed by a sensation of numbness. Easily soluble in water and alcohol 95%: insoluble in solvent ether and benzene.

Injectio Amethocainæ Hydrochloridi (*Inj. Amethocain. Hydrochlor.*).—A sterile solution of Amethocaine hydrochloride in injection of sodium chloride, prepared by dissolving the contents of a sealed container having 88.5 to 110% of $C_{15}H_{24}O_2N_2HCl$.

Dose as of Amethocaine Hydrochloride.

4. **BUTACAINÆ SULPHAS** (*Butacain. Sulph.*), Butyn,
 $(C_{18}H_{30}O_2N_2)_2H_2SO_4$.

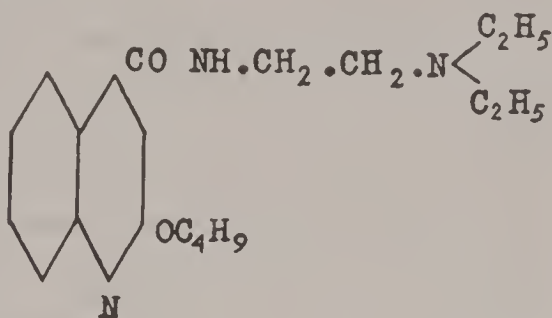
Butacaine sulphate is sulphate of the base, γ -di-*n*-butyl-amino-propyl-*p*-aminobenzoate, prepared by the interaction of 1-chloro-3-di-*n*-butyl aminopropane and sodium *p*-aminobenzoate.



A white inodorous crystalline powder, with slightly bitter taste followed by temporary insensibility of the tongue. Soluble at 15.5° in less than 1 water and soluble in warm alcohol (95%) and in acetone: slightly soluble in chloroform and insoluble in solvent ether.

5. **CINCHOCAINÆ HYDROCHLORIDUM** (*Cinchocain. Hydrochlor.*), $C_{20}H_{29}O_2N_3HCl$, Nupercaine.

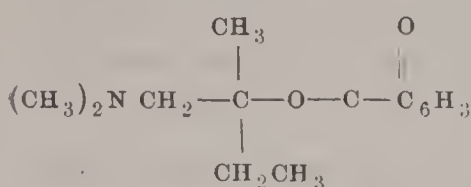
Cinchocaine hydrochloride is the hydrochloride of beta-diethyl aminoethylamide of 2-butyloxy-cinchoninic acid and chloride acting with *asym*-N-diethylethylenediamine, treating with sodium butylate and conversion of the base into hydrochloride.



It contains not less than 97.5% of $C_{20}H_{29}O_2N_3HCl$ substance being dried for 6 hours over sulphuric acid.

Fine white, inodorous, hygroscopic crystals soluble at 15.5° in 0.5 of water and soluble in alcohol (95%), acetone and in chloroform.

6. **AMYLOCAINÆ HYDROCHLORIDUM** (*Amylocain. Hydrochlor.*), Stovaine hydrochloride, $C_{14}H_{21}O_2N_2HCl$. (Not official).



It is the hydrochloride of the benzoyl ester of methylethyl dimethylamino methyl carbinol, prepared by the action of magnesium ethyl bromide on dimethylamino-acetone. A colourless, crystalline powder with a slightly bitter taste followed by a

feeling of temporary numbness. Soluble in 2 of water (making a faintly acid solution), and in 3 of dehydrated alcohol.

Dose, $\frac{1}{3}$ to $\frac{3}{4}$ grain or 0.02 to 0.05 gramme orally or subcutaneously and $\frac{1}{3}$ to $1\frac{1}{2}$ grains or 0.02 to 0.1 gramme intrathecally.

Pharmacology [and Therapeutics]

Cocaine has *local action* on (i) *tissues in general* and (ii) *especially on the sensory nerve endings*: (iii) in addition it has *systemic action* after absorption, more marked on the central nervous system.

(1) Cocaine is a **protoplasmic poison** : even in a dilution not sufficient to paralyse the nerve-endings, it paralyzes the nerve cells. By its intravenous administration, it causes disfunction of the vital centres and death with a smaller dose than is necessary for generalised anæsthesia. Superficial cells, leucocytes and spermatozoa are readily paralysed and given by subcutaneous injection for local anæsthesia, it may cause tissue necrosis.

Cocaine has no action on the intact skin as it does not penetrate to reach the sensory nerve endings. Even a 15% ointment causes only a slight lowering of skin sensation.

(2) Applied directly on any nerve endings even in 1 in 500 solution, cocaine paralyzes them without any stage of initial stimulation. This action is more marked on the **sensory nerve-endings** especially on those conveying the **pain and touch sense** but not the **temperature sense**. A more concentrated solution paralyzes the **motor nerve-endings** after the sensory, but these recover earlier.

Applied directly on any mucous membrane as of the nose, eyes, pharynx, œsophagus, stomach and rectum also urethra, vagina and bladder or injected subcutaneously in $\frac{1}{2}$ to 2% solution, it causes **local anæsthesia**. A more widespread anæsthesia may be produced if injected into a nerve trunk and even more so, into the subdural canal. Thus, if injected between the 3rd and 4th lumbar vertebræ, the lower limbs are anæsthetised upto the umbilicus without motor paralysis.

The anæsthesia is maintained as long as cocaine is left there. This is usually 30 minutes. Unless the place is highly vascular, it is slowly absorbed and removed from the site of application and the normal sensation gradually returns. Cocaine is a **vasoconstrictor** which by reducing the local circulation, hinders diffusion of the drug and helps to prolong the anæsthesia. This is further helped by combining it with a dilute solution of adrenaline chloride which being a stronger vasoconstrictor, lessens the local circulation even more. As cocaine is readily adsorbed by the tissue colloid, a slow absorption favours such a process and allows sufficient time for elimination also. Cocaine is thus prevented from concentrating in the general circulation in a toxic dose.

[Cocaine hydrochloride and other local anæsthetics of this group in *watery solution* are conveniently utilised for a large variety of *surgical operations*, superficial or deep. Cocaine alkaloid in fatty or oily bases has been used as *suppository*¹⁰² : *ointment* or *oily spray*⁴⁰⁸ for painful conditions in the mucous

(402) R
Chlorbutol gr. 5
Cocain. gr. 1
Ol. Theobrom. gr. 30
Suppository for painful piles.

(403) R
Chlorbutol gr. 10
Cocain. gr. 2
Eucalyptol min. 20
Phenol. gr. 1
Paraff. Liq. Lev. ad. fl. oz. 1
Throat spray.

membranes or in the skin. Cocaine hydrochloride is made into *eye discs*, *pastilles* and *lozenges*⁴⁰⁴ and used for eye and throat affections].

EYE.—In addition to (a) causing **local anæsthesia** (which is superficial and may not extend to the iris) and also (b) **vaso-constriction** (blanching extends deeper), (c) it dilates the **pupil**, probably by stimulating the cervical sympathetic nerve-endings. This dilatation is partial as atropine dilates it further. The **accomodation** is slightly impaired, but the light reflex is retained. The **intraocular tension** is often lowered but may sometimes be increased.

[Cocaine in 3 to 4% solution⁴⁰⁵⁻⁴⁰⁷, is a popular local anæsthetic for many eye operations. A sterilised watery solution is simply dropped into the conjunctiva and in 5 minutes the anæsthesia is complete].

How cocaine acts is uncertain; either paralyzes the sensory nerve endings just like curare acting on the motor endings or it is a selective nerve poison.

AN IDEAL LOCAL ANÆSTHETIC

(i) *Should be* effective in a moderate dose and have local selective anæsthetic action only.

(ii) Freely soluble in water and the solution capable of sterilisation by boiling: a cocaine salt slightly decomposes on prolonged boiling.

(iii) It should be of low toxicity and not cause local irritation or necrosis at the site of injection and anæsthesia should be of short duration: cocaine being a protoplasmic poison, is fairly toxic to the tissues at the site of application, especially in a concentrated solution.

(iv) *It should not be* habit forming; cocaine causes drug habit if taken frequently orally.

Therefore it became necessary to look for less toxic substitutes and many synthetic compounds have recently been introduced in practice. These are tertiary aminoesters of aromatic acids. Although cocaine is often the first choice for anæsthesia of mucous membranes, for subcutaneous infiltration, it has lost much grounds. Many of the newer compounds are of low toxicity, rapidly destroyed by the liver if absorbed and have no cumulative effect. So these are more frequently used parenterally.

(404) B

Cocain. Hydrochlor. gr. 1/16

Acid Benz. gr. 1

Menthol gr. $\frac{1}{4}$

Sucros. gr. 2

Pulv. Trag. Co. q.s.

Throat lozenge.

(405) B

Liq. Adrenal. Hydrochlor.

min. 10

Cocain. Hydrochlor. gr. 5

Aq. Steril. min. 120

For conjunctival anæsthesia.

(406) B

Cocain. Hydrochlor.

Zinc. Sulph. aa. gr. 2

Aq. fl oz. 1

Eye lotion for conjunctivitis.

(407) B

Cocain. gr. 8

Ol. Ricin. fl. oz. 1

Eye drop.

(St. George's)

(i) **PROCAINE** (novocaine) is best for causing local anæsthesia by **injection**. It is non-irritant, acts promptly, the effects are moderately lasting especially if combined with adrenaline and is absorbed slowly : if absorbed, is detoxicated by the liver and other tissues and readily eliminated by the kidneys. Thus its toxicity intravenously is $\frac{1}{4}$ th of cocaine and subcutaneously 1/10th. But it has *poor penetrating power* and is unsuitable for anæsthetising a mucous membrane by local application.

The B.P. weak injection of procaine and adrenaline is used for *infiltration* on a moderately big area and the strong injection for *subcutaneous injection* as for extracting a tooth. For *intra-theccal administration* procaine 2 to 5% with dextrose 5% is used. The maximum dose is 0.15 g.

A 0.1% solution of procaine hydrochloride 4 mg./kg. *intravenously* given in 20 minutes, has been used to relieve pain of traumatic, post-operative and of malignant disease successfully. The safety lies in its adequate destruction in the system. The patient may get a sensation of warmth, flushing of the skin of the face and neck, dry mouth, mydriasis, light headedness and a feeling of relaxation (Graubard, 1947). It is a *cardiac depressant* (quinidine action) and should be used with caution in heart disease.

Available as 2% solution or tablet with adrenaline. **PLANOCAINE** is available as powder : 2% solution in ampoule and tablets (with adrenaline).

(ii) **AMETHOCAINE** is a local anæsthetic like procaine but is 5 times **more toxic** : the advantage claimed is that it is 15 times stronger than procaine and 10 times the activity of cocaine and a weaker strength of it is sufficient. In 1 to 2% sol. is used for **surface anæsthesia** in ear, nose and throat : 0.066% sol. for **spinal anæsthesia**, total dose 5 to 20 mg. and 0.01 to 0.1% sol. for **infiltration anæsthesia**. In ophthalmology 0.5% sol. is used but may cause irritation and haziness of the cornea. For urethra 0.1% solution and for rectum 3% suppository are used. Amethocaine used by injection should be combined with adrenaline solution which lessens toxicity.

Available as **ANETHAINE** in powder, 2% ampoules and 1% ointment.

(iii) **BUTACAINE** has the same systemic toxicity as cocaine but subcutaneously butacaine is more toxic. It however easily penetrates mucous membranes, causing rapid **surface anæsthesia** and action is more prolonged than cocaine. On the eye, it does not cause ischæmia nor damages the cornea. It does not dilate the pupil nor affect accommodation. It is mainly used for eye work in 2% solution or as ointment. It may also be used for nose and throat work.

(iv) **CINCHOCAINE** is 6 times as toxic as cocaine by intravenous injection and 5 times as toxic subcutaneously but has a higher (10 times) anæsthetic property, especially on the mucous membranes. It is thus most potent of the local anæsthetics : used by **injection** and for **surface anæsthesia**.

(a) *By injection* 0·05 to 0·1% solution (maximum quantity, 100 ml.) : (b) to cause *surface anæsthesia*, for cornea 0·1% : for nose and throat : 0·5 to 2% : for infiltration 0·05 to 0·2% with adrenaline chloride and for skin as ointment 0·5 to 1% of it should be used. (c) *Lozenges* each containing 1 mg. are used prior to laryngoscopic, bronchoscopic and gastroscopic examinations. (d) For *spinal anæsthesia*, 0·5% solution in 6% dextrose (7·5 to 10 mg.) may be used. (e) Being soluble in oil, it may be used as *suppository* or *ointment*. Cinchocaine is readily destroyed by the liver and only moderately toxic to the tissues.

Nupercaine is available in 0·1%, 0·15% and 0·5% solution with adrenaline also as 0·05 g. and 0·1 g. tablets : also 10% lubricant for instrumentation.

(v) **AMYLOCAINE** (*Stovaine*) is a local *anæsthetic*, being rapidly absorbed from oral or subcutaneous administration and rapidly destroyed in the liver. Local application on the mucous membrane is less effective than cocaine. But its main use is a *spinal anæsthetic* and the total dose is 20 to 60 mg.

ANOCI-ASSOCIATION.—During a surgical operation, it is necessary to prevent all afferent impulses especially those of pain from reaching the brain otherwise the reflex shock affects the medullary centres (Crile). A general anæsthetic completely blocks the emotional (psychic) but to a less extent, the traumatic shock whereas a local one blocks the latter only. A complete blocking of all afferent impulses or noci-association is required to have a shockless surgical operation.

(3) **CENTRAL NERVOUS SYSTEM.**—Even in a comparatively moderate dose as 1 grain, cocaine causes some **general excitation** of the whole of the central nervous system, more markedly of the superior psychic centres and the motor areas of the brain and to a less extent, of the brain-stem including the medulla and spinal cord. Given in bigger doses, the lower centres are more affected than the cerebrum. This initial stimulation is followed by depression of the successive centres.

Thus its action is somewhat like that of caffeine but it is less powerful on the **superior psychic centres**. The subject is more cheerful and talkative and his judgment and general mental capacity are somewhat increased. He is wakeful and sometimes insomnia may be marked. But the mind wanders from one subject to another without sufficient concentration for any length of time and in spite of a feeling of excitement, he does not wholly lose self-control. His power of endurance and capacity for muscular work are increased : further, cocaine being anæsthetic to the stomach, he has less sense of hunger and is less easily fatigued. Cocoa leaves are chewed by some of the natives of South America as a restorative after fatigue and hunger.

There is a general **tendency to movement** and although co-ordinate with a small dose, a bigger dose causes certain amount of inco-ordination and tremor. The mental power is somewhat depressed. With a still bigger dose, a generalised narcosis follows and then convulsion : the site of action probably

is in some portion of the hind brain. These are due to stimulation of the motor cortex of the brain and also probably, to a less extent of the lower motor centres. Finally, these are paralysed and coma sets in.

MEDULLA is **stimulated** in the beginning. The respiration becomes quicker and deeper but shallower if much quickened. There is marked vaso-constriction raising the blood pressure.

SPINAL CORD is also *stimulated* causing increased tendon reflexes and with a bigger dose, strychnine type of convulsion.

Depression follows in the same order, a descending stimulation-depression, ending finally in collapse: the respiratory centre in the medulla is depressed: breathing becomes slow and shallow or Cheyne-Stoky and finally, death follows.

The excitement from cocaine is entirely different from that following the narcotics of the alcohol group. With alcohol, there is no real stimulation at all in any stage but with cocaine, there is as shown by,

- (i) Increased reflexes (alcohol diminishes reflexes).
- (ii) Diminished reaction time following stimulation (alcohol increases it).
- (iii) Greater excitability of the motor cortex to electrical stimuli (alcohol diminishes the excitability).
- (iv) Real stimulation of the lower centres as those in the medulla.

(4) SYMPATHETIC NERVOUS SYSTEM.—Cocaine increases the response of the sympathetically innervated organs to adrenaline: this is probably due to its inhibiting amine oxidase which destroys the injected adrenaline.

(5) CIRCULATORY SYSTEM.—With a small dose, the heart is temporarily slowed and blood pressure rises from stimulation of the **vaso-motor** (vaso-constriction) and **vagal centres** in the medulla. With a moderate dose, this rise of pressure is still maintained, but the pulse quickens, the vagal centre and the endings being paralysed. But more probably this is due to stimulation of the **acceleratory sympathetic centre** and directly of the **heart muscles**. But with bigger doses, both the medullary centres and the heart muscles are depressed resulting in collapse and finally death.

(6) TEMPERATURE is slightly *raised* from the increased motor activity and to some extent from direct action on the *heat regulating centre*.

(7) ALIMENTARY SYSTEM.—Cocaine, in small doses, **increases the peristaltic movements** of the stomach and the intestine by stimulating the Auerbach's plexus but a big dose causes their paralysis. The **glandular secretions** are slightly diminished.

ELIMINATION.—URINE in some cases is **increased** and in others diminished, probably due to vascular cause. Other secretions are slightly decreased.

Cocaine is partly oxidised and destroyed in the liver but is largely excreted unchanged in the urine.

TOLERANCE of a moderate degree is obtained by repeated and frequent intake causing ultimately cocaine habit.

Acute Cocaine Poisoning.—The symptoms are of mental confusion and excitement, dilated pupils, feeble quick pulse, irregular respiration, vomiting and sometimes a rise of temperature. In severe poisoning, convulsion passes on to unconsciousness, collapse and death from respiratory failure. The usual fatal dose is about 8 grains given intravenously although 1·5 grain has been known to have caused death.

Treatment.—*Excitement* or convulsion may require pentothal sodium intravenously: for *respiratory failure*, oxygen, CO₂, and analeptics are indicated.

COCAINE HABIT.—Cocaine is mostly taken with betel leaves. As sufficient tolerance is not established, continued indulgence causes rapid physical, mental and moral deterioration. Pulse and respiration are quickened and the pupils dilated. Salivation is often present. Appetite is lost and the body rapidly wastes. Sleeplessness, tremors, sensation of insects creeping about and in some cases, convulsion may follow. Hallucination and delirium are common. Power of mental concentration, of discrimination and memory are lost. Moral perversion of various kinds follows to end finally in insanity.

Treatment is withdrawal of the drug which unlike morphine is easier and also symptomatic measures.

VARIOUS METHODS OF PRODUCING LOCAL ANÆSTHESIA

As intravenous administration is very toxic, when cocaine is administered by subcutaneous injection, care should be taken to avoid a vein. Further, a barbitone has been found to antagonise toxic action of cocaine (Hofvenedahl): 0·5 gm. of sodium barbitone may be given orally one hour before causing local anæsthesia.

(i) **Direct application.**—A 2 to 4% solution of *cocaine hydrochloride* is the best for anæsthetising the eye, and for throat (5%): nose and larynx (10%): and occasionally for urethra and the bladder (1 to 2%), but the total quantity should not exceed 0·1 gm. *Butyn*, (2% solution), *holocaine* or *phenacaine* (1% solution): and *amethocaine* (0·5 to 1% solution) have nearly the same penetrative power and are used for cocaine: *nupercaine* is useful in weaker solution (p. 574). *Novocaine*, *eucaine* and *alypin* are less effective.

An ointment in collapsible tube of *anethaine* and *nupercaine* 1% is available: antipruritic and analgesic.

(ii) **Subcutaneous injection.**—Owing its low toxicity, *procaine* or *novocaine* is preferred. The strength of the solution should not exceed 2% (may be even 0·5%) and the profitably combined with a dilute solution of adrenaline hydrochloride. *Amethocaine* 0·5% solution may be used. *Butyn* and *nupercaine* (p. 574) may also be used.

Quinine urea hydrochloride in 0·5 to 1% solution is occasionally injected as anæsthetic especially into the piles: effect although feeble, is of fairly long duration but may cause tissue necrosis.

(iii) **Regional, conduction or block anæsthesia.**—*Procaine* in 2% solution is injected close to the nerve trunk and anæsthesia follows in the whole area of its distribution. The total quantity should not exceed 0.2 gm. *Stovaine* and *alypin* are powerful anæsthetics but irritant.

(iv) **Infiltration anæsthesia** (Schleich).—*Procaine* in very dilute solution in normal saline solution containing 0.1% procaine, 0.8% NaCl and 0.001% adrenaline hydrochloride or the B.P. weak injection is given subcutaneously at different points in the area to be anæsthetised. *Amethocaine* and *Cinchocaine* are also used. The œdema and pressure so caused also help the anæsthesia. The infiltration may be continued deeper. This is suitable for anæsthetising a large area as required in bigger operations : procaine or amethocaine is preferable but the total quantity should not exceed 0.4 g. of procaine and 0.25 g. of amethocaine.

(v) **Spinal anæsthesia.**—This causes a special type of *block anæsthesia* involving all kinds of nerve fibres, sensory, motor, somatic and autonomic and is risky on account of motor paralysis especially of respiration also occasionally paralysis of the bladder and fall in blood pressure with collapse and tendency to hæmorrhage.

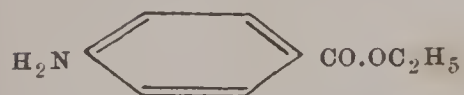
The solutions usually used are (a) *amylocaine hydrochloride* and *sodium chloride* each 100 mg. in 1 ml. of water for injection with sp. gr. of 1.08 (*Chaput's solution*) or (b) *amylocaine hydrochloride* and *dextrose* each 50 mg. in 1 ml. of water for injection (*Barker's solution*) with sp. gr. of 1.023. Dose of amylocaine hydrochloride is 20 to 60 mg., may be combined with ephedrine hydrochloride 60 mg. or methylamphetamine hydrochloride 15 to 30 mg. as protection against circulatory and respiratory failure. In a few minutes anæsthesia is established which continues for one hour or more. Amylocaine is less toxic than cocaine and is safer : persistent headache and vomiting follow in some cases. (c) *Procaine* and *Cinchocaine* are also used and fairly safe. A solution of 200 mg. of procaine hydrochloride in 5 ml. of water for injection with 5 minims of pitressin is a suitable preparation.

(vi) **Caudal Anæsthesia.**—The local anæsthetic (one of those used in spinal anæsthesia) is injected into epidural space through a needle into the caudal canal either intermittently or in continuous drip : suitable for pelvic, genital and perineal operations.

SUMMARY.—Cocaine is a powerful local anæsthetic but for its toxicity, local on the tissues of contact and systemic especially on the nervous system, (a) it is now mainly used for localised surface anæsthesia of the eyes and of certain mucous membranes. (b) For wider application parenterally, several synthetic preparations have been introduced with equal or more intensive anæsthetic property, used in more dilute solution with less toxic reactions.

Other Cocaine Substitutes

1. BENZOCAINA, (*Benzocain.*), Ethyl Aminobenzoate, Anæsthesine $C_9H_{11}O_2N$.



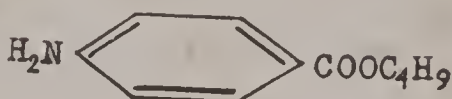
Ethyl *p*-aminobenzoate is prepared by the reduction of ethyl *p*-nitrobenzoate. A white crystalline powder with a slightly bitter taste

which is followed by a sensation of numbness. Soluble at 15.5° in 2500 of water, in 8 of alcohol (90%), in 4 of solvent ether, in 2 of chloroform and in 50 of fixed oils.

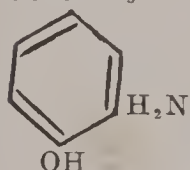
2. BUTYLIS AMINO BENZOAS (*Butyl. Aminobenz.*), Butyl Aminobenzoate, $C_{11}H_{15}O_2N$

Butyl Aminobenzoate, *n*-butyl *p*-aminobenzoate, prepared by the interaction of *n*-butyl chloride and sodium *p* aminobenzoate. A white crystalline, inodorous tasteless powder, very

slightly soluble in water but soluble in dilute acids, alcohol (95%), chloroform, solvent ether and in fatty oils



3. ORTHOCAINA, (*Orthocain.*), Orthocaine, Orthoform $C_8H_9O_3N$



Orthocaine is methyl ester of *m*-amino *p* hydroxy benzoic acid, prepared by esterifying with methyl alcohol the reduction product of 3-nitro-4-hydroxy benzoic acid.

A white or faintly yellow, inodorous, crystalline powder, soluble at 15.5° in 2500 parts of water. Soluble in 7 of alcohol (90%), in 50 of solvent ether, and freely in caustic soda solution.

Pharmacology [and Therapeutics]

(1) BENZOCAINE is an insoluble local anæsthetic with 1/10th toxicity of cocaine and has thus a wide field of utility (a) as *lozenges* in painful conditions in the mouth and throat also preliminary to laryngoscopy, bronchoscopy and gastroscopy: (b) as *dusting powder* (10 to 50% of benzocaine in talc) in various superficial painful ulcerations and unrelieved pruritus: (c) as *insufflation* with adrenaline or atropine in nasopharyngeal allergy: (d) as *injection* in oily solution for anal fissure⁴⁰⁸ also (e) as *bougies*, *pessaries* and *suppositories* each containing 5 grains and as 10% *ointment*⁴⁰⁹.

Internally benzocaine in 3 to 5 grain or smaller divided doses is prescribed for vomiting⁴¹⁰ and gastric pain.

(408) B

Benzocain. gr. 15

Alcohol Benzyl. min. 20

Æther Anæsth. min. 48

Ol. Arach. ad. fl. oz. 1

Inj. for local painful conditions.

(409) B

Benzocain. 10

Ung. Hamam. 45

Ung. Zinc. Oxid. 45

Ung. For bleeding piles.

(2) BUTYL AMINO BENZOATE is an insoluble local anæsthetic with a prolonged action. It is used as *dusting powder* with talc, *ointment* and *solution* in oils and in alcohol or as *suppository* of 1 gr. each. If used for a long time, it may cause dermatitis.

(3) ORTHOCAINE is used locally as anæsthetic, being made into *dusting powder* with talc, *ointment* (5 to 10%)⁴¹¹ and as *insufflation* in tubercular laryngitis. Orthocaine may sometimes cause severe irritation even tissue necrosis.

SUMMARY.—*Insoluble* local anæsthetics as benzocaine, butyl aminobenzoate and orthocaine are used for **local action** as dusting powder, ointments and suppository and sometimes as injection dissolved in oil, as insufflation, lozenges and orally as gastric sedative. These have prolonged action without much toxicity.

Non-official Preparations

BENZAMINE LACTATE, also called Beta-Eucaine lactate, is soluble in water, can be boiled and has about 1/5th toxicity of cocaine.

Unlike cocaine it does not constrict blood-vessels, nor dilates pupils. The anæsthetic action slowly develops. It does not go well with adrenaline chloride solution and therefore the anæsthesia is of shorter duration. Its borate (BETA-BOROCAINE), is more useful.

PERCAINE, 1 to 2% solution has been recommended for the mucous membranes and in 0.1% solution is used for infiltration and spinal anæsthesia.

PHENACAINE or HOLOCAINE HYDROCHLORIDE, in 1% solution is used for painful eye conditions for causing surface anæsthesia.

ALYPIN, in $\frac{1}{4}$ to 2% solution is used as substitute for cocaine.

PONTOCAINE or TETRACAINE, 0.5% solution is used for the eye : 2% solution for nose or throat : 10 to 20 mg. made into 1% solution used for spinal anæsthesia.

LAROCAINE HYDROCHLORIDE, 2 to 5% solution for the eye : 5 to 10% solution for nose or throat and 0.75 to 1% solution for urethra : for conduction anæsthesia, 0.25 to 3% solution with adrenaline chloride.

INTRACAINE is used for procaine in half strength.

Aromatic Alcohol

ALCOHOL BENZYLICUM (*Alcoh. Benzyl.*), $C_6H_5 \cdot CH_2OH$



CH_2OH

Benzyl alcohol is prepared by the alkaline hydrolysis of benzyl chloride containing not less than 97% w/w of C_7H_5O .

A colourless, nearly inodorous liquid with a sharp, burning taste. Soluble in 25 of water : readily miscible with alcohol (95%), chloroform and with solvent ether.

Benzyl alcohol is used in the preparation of *Injectio Ethanolaminæ Oleatis*.

Benzyl alcohol is aromatic and is occasionally used in perfumery.

(410) B

Anæsthesin. gr. 2

Chlorbutol gr. $2\frac{1}{2}$

Phenobarbiton. gr. $\frac{1}{4}$

Pulv. For vomiting of pregnancy.

(411) B

Orthoform. 10 to 20

Adrenalin. 0.005

Paraff. Moll. Alb. 100

Ung. For inflamed piles.

It is moderately **anæsthetic** and is used as ointment or lotion for cutaneous itching⁴¹². For injection and topical application on the mucous membrane, 4% solution in water may be used but not very suitable.

It is comparatively non-toxic and readily converted into hippuric acid in the body.

PROCTOCAINE has procaine 1.5, butyl-*p*-aminobenzoate 6, benzyl alcohol 5 and vegetable oil to 100 : this given by injection in anal fissure, anal spasm also myalgia, sciatica and other neuralgias. The effect is almost immediate and lasts for about 21 days : available in 2, 5 and 10 c.c. ampoules.

DRAMAMINE (beta-dimethyl-aminoethyl benzohydrylether-8 chloro-theophylline) in 100 mg. capsule has been found useful in *sea-sickness*, one before each meal and one at bed time.

F. Drugs Acting on the Autonomic Nervous System

The activities of the autonomic nervous system, as distinguished from the cerebro-spinal system, are not controlled by the conscious mind and may act without cerebral control (*autonomic*). These supply the various involuntary muscles and all the secretory glands.

There are *two groups* of autonomic nerves almost antagonistic to one another in function.

(i) The nerves of the **parasympathetic system** arise (a) from the mid-brain and the medulla and accompany the various cranial nerves. (b) Some of these also arise from the sacral region and are distributed along with the 2nd, 3rd and the 4th sacral nerves.

(ii) The nerves of the **sympathetic system** arise from the first dorsal to the third lumbar segments and are associated centrally with the respective motor and sensory roots of the cerebrospinal system. Peripherally, they have cell-stations in the sympathetic ganglia and in the cardiac, solar and the hypogastric plexuses. The cell-stations are also sometimes present near the place of their distribution.

The parasympathetic and sympathetic systems have *antagonistic* physiological functions and drugs also mostly act in an opposite way on the two systems. Thus bronchial musculature is stimulated by parasympathetic activator physostigmine causing broncho-constriction but is depressed by sympathetic activator adrenaline causing broncho-dilatation. Pupil is constricted by physostigmine and dilated by adrenaline. On this basis, an *augmentation* of function of a particular tissue

(412) B

Alcohol Benzyl.

Alcohol (90%)

Aq. Dest. part. æq.

Antipruritic application.

results from the activation of either the parasympathetic or the sympathetic system : *inhibition* may be due to the activation of the opposite system or due to a drug making the target-tissues insensitive to the parasympathetic or sympathetic activity. Atropine does this to the parasympathetic and ergotoxine to the sympathetic nerve endings.

DISTRIBUTION OF THE AUGMENTORY AND INHIBITORY NERVES

Blood vessels and the Heart : Sympathetic +, Parasympathetic —.

Skin (Erector muscles of the hairs) : Sympathetic +, Parasympathetic —.

Stomach, Intestines and Urinary bladder : Vago-sacral +, Sympathetic —.

Sphincters : Sympathetic +, Sacral —.

Uterus : Sympathetic + and Sacral —.

Iris, circular and Ciliary muscles : Parasympathetic +.

Iris, radial : Sympathetic +.

Bronchial muscles : Vagal +, Sympathetic —.

Secretory glands : Vagal +. The skin glands although supplied by the sympathetic, react pharmacologically to parasympathetic activators. Salivary glands react to both the systems but more to the parasympathetics.

(+ for Augmentory and — for Inhibitory action).

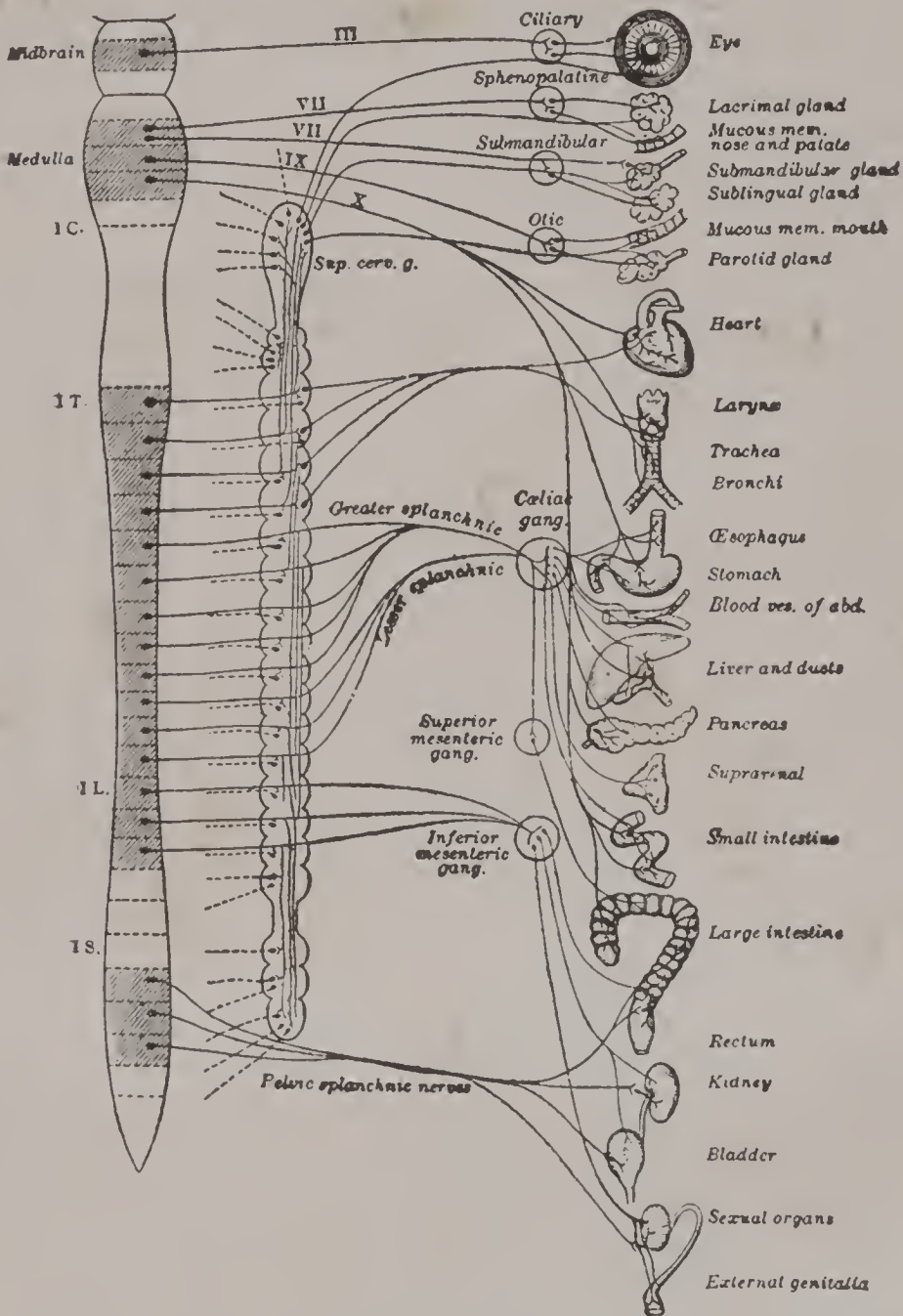
CONTROLLING CENTRES.—Medullary centres regulate the autonomic activities. These are under the hypothalamic centres which adjust the distribution of water and salts and exercise a general control over circulation and metabolism. These again are under cortical control and are affected indirectly by the excitation of emotion (Clark).

The sympathetic nerves are best activated by adrenaline and inhibited by ergotoxine. The parasympathetics are activated by pilocarpine, physostigmine and acetylcholine and inhibited by atropine.

The stimulation of the sympathetic nerves causes secretion of adrenaline and that of the parasympathetic, of acetylcholine. So adrenaline and acetylcholine may be called their specific activating hormones. In fact, it is believed that all autonomic post-ganglionic fibres transmit impulses to their effective cells by chemical means : these are either an adrenaline-like substance or acetylcholine. Dale accordingly called these two sets of nerve fibres as *adrenergic* and *cholinergic*. The drugs acting on the autonomic system, have been classified into four groups, *activators* or *depressors* of one set or of the other.

(i) It has been further shown that an impulse of excitation is transmitted from the pre-ganglionic to the post-ganglionic nerves by acetylcholine, *parasympathin*, (A. Cl.), and to the post-ganglionic endings either by acetylcholine (through the cholinergic or parasympathetic fibres) or by an adrenaline-like substance, *sympathin* (by adrenergic or sympathetic fibres). Again, while all parasympathetic endings are cholinergic and most of the sympathetic endings adrenergic, some of the latter

are cholinergic also as those supplying the sweat glands and certain blood vessels. Motor nerve endplates in the voluntary muscles act by liberation of acetylcholine.



(After Meyer and Gothlieb, from Gray.)

Fig. 37.—The distributions of the *parasympathetics* (in the midbrain, medulla : 3rd, 4th, 9th and 10th cranial nerves and in the sacral regions 2nd, 3rd and 4th sacral) and the *sympathetic* (in the mid-brain, the first dorsal to the third lumbar) to the various involuntary muscles and secretory glands.

It will thus appear that (a) *motor end plate* is stimulated by acetyl choline and blocked by curarine : (b) *motor nerve endings* are blocked by procaine and botulin toxin : (c) *muscles*

are directly stimulated by adrenaline (Brown and others, 1948) and potassium ion (partly).

How the *sensory nerve endings* act is not definitely known. These may also have chemical activators. For transmission of impulses in the *brain*, acetylcholine plays an important part.

An enzyme cholinesterase present in the blood rapidly destroys any acetylcholine that may escape from the site of production by splitting into choline and acetic acid : this is counteracted by physostigmine.

(ii) The function of adrenergic substance is also complex. Sympathin is liberated by the sympathetic nerve ending when activated and a store of it exists in the adrenaline medulla. But adrenaline is not identical with sympathin, latter having a much wider distribution, not causing vaso-motor reversal effect with ergotoxine.

DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM may be grouped as follows.—(i) Those acting on the **ganglia** as conium, gelsemium and nicotine. (ii) Those acting on the **parasympathetic nerve endings**, (a) *stimulating* as muscarine group, choline group, physostigmine and pilocarpine or (b) *depressing* as the atropine group. (iii) Those acting on the **sympathetic nerve endings**, either (a) *stimulating* as adrenaline, ephedrine, amphetamine, tyramine, and other amines or (b) *depressing* as ergotoxine and ergotamine (although these have powerful actions on the uterus, not due to sympathetic depression) and to a less extent, apocodeine and yohimbine.

The above reactions are the characteristics of the *terminal distribution* of the nerve fibres either of one type or of the other. But the **ganglia** react alike, i.e. the same drug either stimulates or paralyses the ganglia of both the systems.

The sum up : **Acetylcholine** is liberated at (i) the central cholinergic nerve endings arising from the nerve cell of the central nervous system : this stimulates a voluntary muscle or an autonomic ganglion and has rapid, short-staying local effect without summation. Similar effects are produced by injection of acetylcholine or a small dose of nicotine and has no muscarine action. This may be called *nicotine type of action*.

(ii) Acetylcholine may also be liberated at the parasympathetic postganglionic nerve endings supplying the involuntary muscles, glands and some blood vessels. The effect is more widespread and lasting : has a latent period and often summation. These may also be produced by an injection of acetylcholine. Atropine counteracts except the vasodilators in the chorda tympani and cholinergic nerves in the intestine and the uterus. These effects are also produced by muscarine and increased by physostigmine but not by nicotine. These may be called *muscarine type of action*.

Sympathin is liberated at the post-ganglionic sympathetic nerve endings, the effects resembling those of adrenaline injection. These are either excitory (*Sympathin E*) or inhibitory (*Sympathin I*). While the heart and blood vessels are excited, intestine, bronchi, coronary blood vessel and urinary bladder are inhibited.

1. Drugs Acting on the Autonomic Ganglia

CONIUM (Not official)

This is seldom used in medicine and is of interest so far as it forms a link among the drugs having paralytic action on the motor system between those having the central action and those with the same on the peripheral nerve endings. Its active principle *coniine*, paralyses all the motor nerve-endings resulting in loss of muscular power. The cardiac ganglia and the ganglia in the course of the vaso-constrictor nerves are first stimulated and then paralysed so that at first the pulse is slowed and the blood pressure is raised but soon the pulse is quickened and the blood pressure falls.

All voluntary and reflex activities of the muscles are lost. The respiration becomes feeble and finally as the respiratory centre and the peripheral nerve endings in the respiratory muscles are paralysed, death takes place from asphyxia.

Coniine is rapidly excreted in the urine and so in poisoning, sometimes death does not take place.

[The tincture, (Dose, 30 to 60 minims), is sometimes given for spasmodic conditions like whooping cough and asthma. An ointment of the extract containing 0.1% of the alkaloid, is used for anal fissure].

GELSEMIUM (Not official)

Gelsemium is the root of Yellow Jasmine, having a powerful alkaloid, *gelseminine*.

TINCTURA GELSEMI.—The root 1, percolated with alcohol (60%) 10.

Dose, 5 to 15 minims.

GELSEMININE HYDROCHLORIDE.—Dose, 1/60 to 1/20 grain.

In toxic doses, it acts as a powerful depressant to the autonomic ganglia and peripheral motor nerve endings like coniine, except that it does not cause any initial rise of blood pressure. All the eye-muscles are paralysed. There may be diplopia, paralysis of accommodation, dilatation of the pupil and drooping of the eyelids. Applied locally into the eye, the pupil is dilated, the action resembling atropine, but causes more irritation.

In a moderate dose, the medullary centres are not affected. But in big doses both the heart and the respiratory centres are involved so that the pulse becomes quick and irregular and the respiration slow, feeble and ultimately stops entirely and death follows from asphyxia.

Towards the end, all the muscles of the body are more or less paralysed. As the cerebrum is not affected, consciousness is retained till the end.

It is sometimes used to relieve neuralgic pain⁴¹³ and spasmodic muscular contraction as of migraine and dysmenorrhœa.

(413) B

Sodium Brom. gr. 10

Tinct. Gelsem. min. 10

Butylchloral Hydr. gr. 5

Aq. Chlorof. ad. fl. oz. 1

One every 4 hours for neuralgia.

NICOTINE (Not official)

This is the alkaloid of the common tobacco. It acts on the *central nervous system*, all *autonomic ganglia* and the *nerve endings* in the voluntary muscles. At first it more or less excites all cells of the nervous system but subsequently depresses them. The *voluntary muscles* show a temporary increase of activity which is soon succeeded by intense muscular weakness. Its most characteristic action however is on the *autonomic ganglia*: their stimulation is followed by paralysis. Stimulation of the preganglionic fibres, therefore produces no result although the postganglionic fibres are unaffected.

Centrally, the *entire cerebro-spinal system* is first excited, followed by paralysis. There is transitory cerebral excitement; in the medulla, the respiratory centre is first stimulated and then paralysed, death following from respiratory failure.

The spinal cord is also stimulated: the reflexes are exaggerated and there may be convulsions.

The action on the autonomic ganglia, stimulation followed by paralysis on big doses is referred to as *nicotine type of action*. From stimulation of the *vagal ganglia*, the pulse is slowed; if this inhibitory mechanism is blocked by atropine, from the action on the sympathetic ganglia, the rate is increased and there is vaso-constriction and rise of blood pressure. But stimulation is quickly followed by paralysis: the pulse rate is increased, blood vessels are dilated and the blood pressure falls. Excessive habitual indulgence of tobacco causes trachycardia and occasionally angular pain.

Respiration is at first quick and feeble afterwards quick and deeper. Later on, the breathing is interrupted, becomes weaker still and finally stops and death follows from asphyxia. These are partly due to paralysis of nerve endings in the diaphragm (curare-like action).

Bronchial muscle is temporarily constricted (stimulation of the ganglia on the course of the vagal fibres) and then dilated (their paralysis and stimulation of the sympathetic ganglia).

The *pupil* is at first contracted but afterwards dilated. Excessive tobacco smoking sometimes causes toxic amblyopia.

Unstriated muscles of the alimentary canal are at first inhibited, followed by their increased activity, shown by vomiting and purging (stimulation of the sympathetic, followed by their paralysis and vagal overaction). Urinary bladder is contracted causing frequent micturition: uterus contracts causing abortion if pregnant.

Glandular secretions are at first increased and then diminished (stimulation followed by paralysis of the secretory nerve ganglia).

LOBELIA (Ind. Pharm. List)

This is the dried aerial parts of *Lobelia inflata*.

This is also called Indian tobacco, obtained from North America.

The stems are rounded, channeled, ovate, with narrow wings and scarred, often of a purplish tint. The leaves are irregularly toothed and hairy. The capsules are inflated, often containing brown seeds. Its active principle is an oily volatile alkaloid, *lobeline* which smells irritating like tobacco. The taste is at first slight afterwards burning and acrid. There is another alkaloid also, *lobelidine* and also *lobelic acid*.

Dose, 1 to 3 grains or 0.06 to 0.2 gramme.

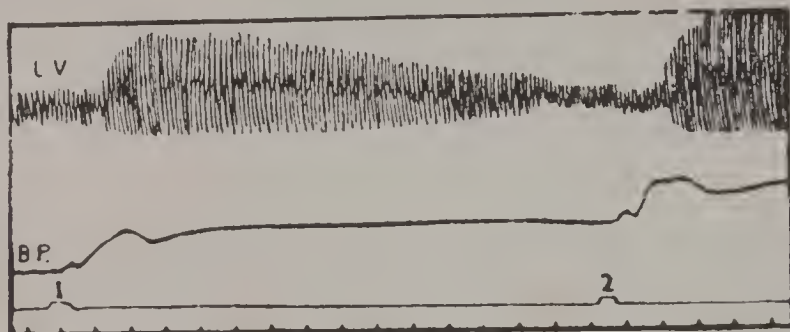
Tinctura Lobellæ Ætherea (*Tinct. Lobel. Ether.*), Percolate lobelia 200 g. in moderately coarse powder with spirit of solvent ether 1000 ml. (1 in 5).

Dose, 5 to 15 minims or 0.3 to 1 ml.

Lobeline resembles coniine and nicotine in action. It first stimulates and then depresses the *vagal ganglia* from which originate the nerves supplying the bronchial muscles: after a temporary constriction, the bronchioles are relaxed. It also stimulates the *carotid sinus reflex* causing

dilatation of the bronchioles and easy respiration [and for this *antispasmodic* action ^{414, 415} lobelia is frequently used in bronchial asthma]. It is also a mild *expectorant*.

A 5 to 10 mg. dose of lobeline hydrochloride lowers the CO₂ threshold, causing marked *stimulation of the respiratory centre* and is prescribed for respiratory failure as from volatile anæsthetics, opium and CO-poisoning. But in toxic doses, it acts like nicotine, paralysing the centre.



(After Dixon)
Fig. 38.—Lung volume (upper) and blood pressure (lower) readings with lobeline injected at 1 and 2. The lung volume immediately increases with broncho-dilatation; as the effect of first dose is disappearing the second was given. Blood pressure also slightly rises (vasomotor).

It is a *gastro-intestinal irritant* and in big doses causes much vomiting and purging. The *heart* is slowed and the blood pressure is raised, but soon depressed and the pulse becomes quick, weak and irregular, (excitation followed by depression of the vagal ganglia).

A moderate degree of tolerance is sometimes established.

LOBELINE (available in 3 mg. ampoules) may be administered *subcutaneously*, *intramuscularly* or *intravenously* in asphyxia, narcotic poisoning and in uncontrollable hiccough occasionally in urticaria, resisting other treatment.

The dose may be repeated if necessary after 15 minutes without danger of accumulation: may be combined with circulatory stimulants.

EUPHORBIA, either as liquid extract or as syrup is used with lobelia and senega as *expectorant* for chronic bronchitis and asthma.

2. Drugs Acting on the Autonomic Nerves

A. DRUGS STIMULATING THE PARASYMPATHETIC NERVE ENDINGS

MUSCARINE GROUP (Not official).—Certain poisonous mushrooms as *agaricus muscarius* contain a poisonous alkaloid *muscarine*. This is important because it *stimulates all the post-ganglionic* or *cholinergic nerve-endings* both in the secretory glands and in the *unstriated muscle fibres* and

(414) R

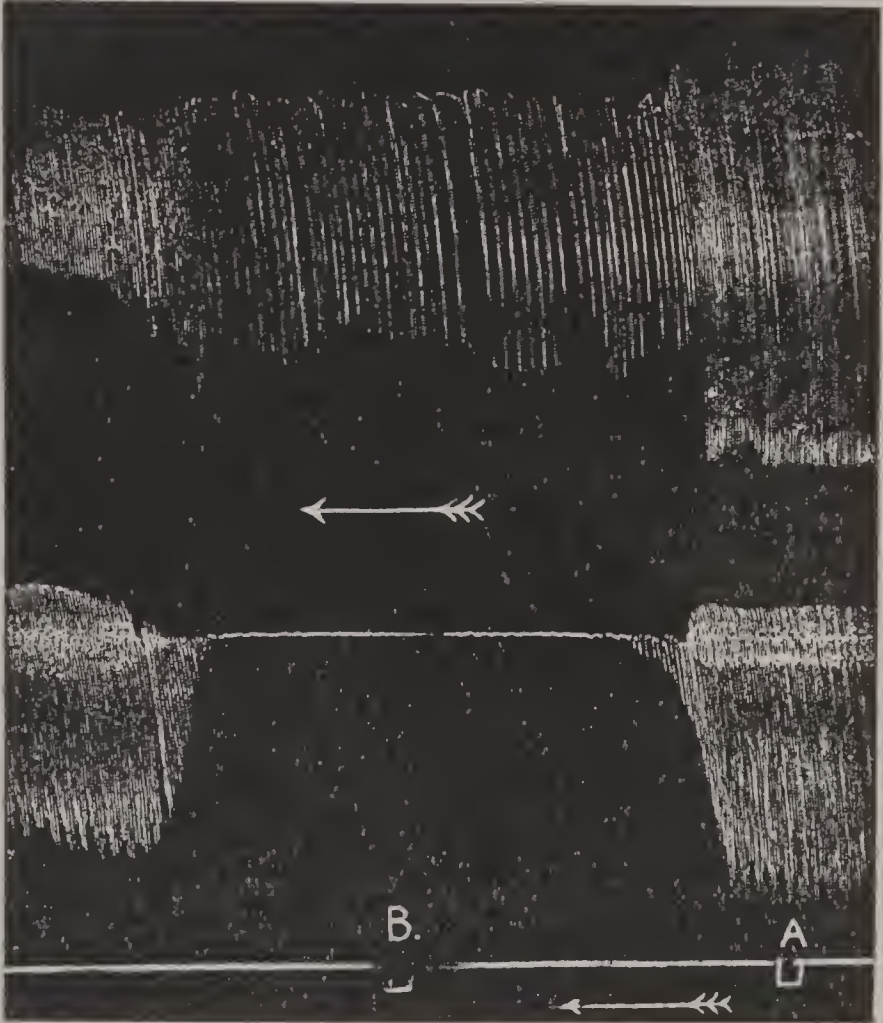
Pot. Iod. gr 3
Tinct. Lobel. Æther.
Tinct. Stramon. aa. min. 15
Tinct. Ephed. Vulg. min. 30
Syr. Tolu min. 30
Aq. Chlorof. ad. fl. oz. 1
For bronchial asthma.

(415) R

Ammon. Bicarb.
Pot. Iod. aa. gr. 2
Sod. Bicarb. gr. 15
Tinct. Lobel. Æther. min. 15
Syr. Vasak. et Tolu. min. 60
Aq. Camph. ad. fl. oz. 1
For chronic bronchitis.

was known long before any other cholinergic preparation was discovered. This action is counteracted by atropine.

The *secretions* of salivary and other mouth glands, lachrymal, nasal, upper and lower respiratory, gastric, pancreatic and intestinal glands are increased.



(Dixon)

Fig. 39.—At A, a small dose of muscarine is given by injection and the auricle is completely stopped in diastole and the ventricle is beating slowly and irregularly (vagal action). At B, atropine is injected and normal heart action is restored.

Involuntary muscles of the stomach, intestine, spleen, bladder, ureters, uterus and bronchi also of the pupil and the ciliary muscles are contracted.

Heart shows vagal inhibition being slowed, acting feebly with lowered blood pressure.

Respiration is not directly affected except through circulation. Contraction of the bronchial muscles may cause much impediment to respiration.

Muscarine is of no therapeutic value.

MEPROCHOL, trade name *Esmodil* 3 mg. subcutaneously or intramuscularly has muscarine action and is used in postoperative atony of the intestine and the bladder.

CHOLINE GROUP

The drugs of this group have lately come into great prominence and some of these as *acetylcholine*, *carbacholum* and *mecholy* are of therapeutic value in increasing and maintaining the tone of the muscles especially of the involuntary muscles.

CARBACHOLUM (*Carbachol.*), $[H_2N.CO.OCH_2.CH_2.N(CH_3)_3]Cl$

Carbachol, called in trade *Chloryl*, *Doryl* and *Moryl*, is carbamylcholine chloride and obtained by the interaction of beta-chloroethyl carbamate and trimethylamine. It contains not less than 99.5% of $C_6H_{15}O_2N_2Cl$, dried at 100°.

Colourless small prismatic crystals or crystalline powder, markedly hygroscopic with a faint odour resembling that of aliphatic amine. Very soluble in water, very slightly so in dehydrated alcohol and almost insoluble in acetone and ether.

Dose, 1/60 to 1/16 grain or 1 to 4 mg. : 1/240 to 1/120 grain or 0.25 to 0.5 mg. by subcutaneous injection.

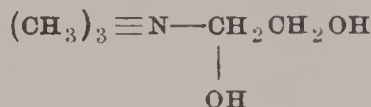
Injectio Carbacholi (*Inj. Carbachol.*), See p. 43.

Dose, 1/240 to 1/120 gr. or 0.25 to 0.5 mg. by subcutaneous injection. If the strength is not stated, one containing 1/240 gr. in 15 min. or 0.25 mg. in 1 ml. shall be dispensed.

Pharmacology [and Therapeutics]

CHOLINE is a derivative of hydroxide of ammonia (NH_4OH) with four hydrogen atoms attached to nitrogen, replaced by three methyl and a hydroxyethyl group.

Choline is present in the blood plasma, one liter containing 160 to 300 mg. combined with lecithin : a small quantity also exists as free choline. It is obtained from food (See p. 296). and is also synthesised, methyl groups of methionine combining with ethanolamine ($NH_2.CH_2CH_2OH$).



Choline has **lipotropic function**. It may promote the transport of fatty acids as phospholipides. This with methionine has been prescribed in hepatic diseases especially in cirrhosis of liver to prevent deposition of fat. Daily dose may be 1 to 2 grm.

The direct systemic action of choline resembles that of muscarine. It slows the heart and increases intestinal movements and glandular secretions.

Certain esters and ethers of choline have both (a) *muscarine type* of action, inhibited by atropine and (b) *nicotine type* of action, inhibited by bigger dose of nicotine : (Dale, 1914). Further, acetyl choline was found to cause (c) contraction of the *skeletal muscles* of amphibia (Riesser). So these have three types of action.

Reid Hunt (1908) found that its ester, acetylcholine was 100,000 times more active than choline itself. It has now

been proved by Loewi (1921) and also by Dale, that acetylcholine is the chemical transmitter of nerve impulse responsible for the cholinergic activities. Vagal stimulation causes an output of acetylcholine.

But acetylcholine is unstable being rapidly hydrolysed to choline and acetate in the presence of an alkali although more stable in acid state as at pH 3.9. Taken orally, this is easily hydrolysed by digestive enzymes. Blood and tissue extracts also do the same on account of these containing cholinesterase and this destruction can be prevented by even a minute dose of physostigmine. Acetylcholine is used in 0.05 to 0.6 g. dose subcutaneously or intramuscularly.



ACETYLCHOLINE BROMIDE is more stable and has been found suitable for therapeutic administration in 0.1 to 0.2 gramme doses subcutaneously and intramuscularly. Acetyl- β -methylcholine or *mecholyl* in 10 to 25 mg. dose subcutaneously and *carbachol* 0.25 to 1 mg. dose subcutaneously are more active. These cause (a) slowing of the heart rate, vaso-dilatation and lowering of blood pressure. (b) Gastro-intestinal movements are increased also (c) gastric secretion along with salivation, sweating and lachrymation especially if given parenterally. These are *muscarine type* of action.

The *nicotine type* of action is less marked.

MECHOLYL is useful in paroxysmal tachycardia of auricular type, Raynaud's disease (vaso-spasm) and in chronic arthritis. The drug as chloride may be used orally, dose 0.2 to 0.5 g. two or three times daily : *hypodermically*, 10 mg. cautiously increased to 20 to 40 mg. in vascular spasm and in auricular tachycardia. For chronic arthritis, *electrophoresis* (p. 20) by putting a solution of metholyl chloride is more helpful. Bromide is less hygroscopic and is more suitable orally but chloride hypodermically is more certain in action.

CARBACHOL (*Doryl*), has been found more stable and not decomposed by body fluid : it may be given orally also (2 mg. tablets, 2 to 4 times daily). It causes more marked contraction of the intestine and urinary bladder, increases gastric secretion and dilates blood vessels : in fact has full parasympathetic stimulation effect. After an intravenous injection, there may be a sense of heat and flushing also sweating, salivation, lachrymation, constriction of the throat and a feeling of

uneasiness in the abdomen ; but these pass off in half an hour. As these do not appear in atropinised patient, carbachol may be used in diagnosis of atropine poisoning. [It is used subcutaneously (0.12 to 0.25 mg.) in postoperative atony of the intestine and urinary bladder : also in paroxysmal tachycardia, peripheral vascular spasm, migraine, Raynaud's disease, intermittent claudication, high blood pressure, glaucoma (applied locally in 0.75% solution), ozæna (locally in 0.5% solution), eclampsia and in chronic arthritis (by ionization). In chronic and less urgent cases, oral administration is good enough. The side-effects are sweating, nausea and fainting attack].

These are *contraindicated* in hyperthyroidism, coronary occlusion, bronchial asthma and in any severe constitutional disorder.

SUMMARY.—The choline group of drugs have powerful muscarine but feeble nicotine type of action : the actions are slowing of the heart, vasodilatation, increased contraction of the unstriated muscle fibres especially of intestine and urinary bladder and increase of glandular secretions. Many of these are unstable and not suitable for therapeutic administration : those stable are administered *hypodermically* (acetyl choline bromide, carbachol and mecholyl chloride), *orally* (carbachol and mecholyl bromide) and by *ionization* (mecholyl).

Mecholyl has more marked action on the heart but *Carbachol*, more on the gastro-intestinal tract and the urinary bladder.

COMMERCIAL PREPARATIONS.—*Carbochol* tablets 2 mg. and ampoule 0.25 mg. in 1 c.c. *Acetyl choline bromide* in 0.05 g., 0.1 g. and 0.2 g. ampoules.

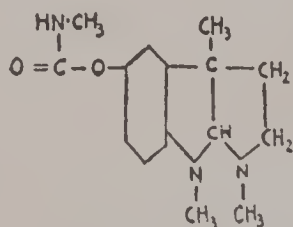
ACETYL-BETA-METHYLCHOLINE BROMIDE in a child of 10 years 0.1 g. : after 2 to 8 days 0.3 g. and after 2 to 3 days, 0.2 g. in the morning and 0.1 to 0.2 g. in the evening after food has been found useful in *megacolon*.

URETHANE-BETA-METHYLCHOLINE CHLORIDE, *Urecholine*, 5 mg. subcutaneously or intramuscularly every 4 to 6 hours has been found useful in postoperative intestinal ileus and retention of urine.

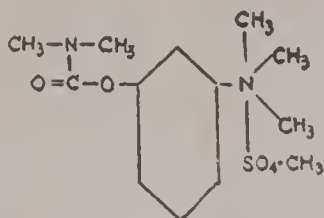
PHYSOSTIGMINE

The alkaloid, *physostigmine* is prepared from the seeds of *Physostigma venenosum*, Calabar bean.

PHYSOSTIGMINÆ SALICYLAS (*Physostig. Salicyl.*), Eserine Salicylate, $C_{15}H_{21}O_2N_3$, $C_7H_6O_3$.



Physostigmine



Neostigmine

Colourless or faintly yellow crystals which become red on exposure to air and light. Soluble at 15.5° in 100 parts of water and more so in alcohol (90%).

DOSE, 1/100 to 1/50 grain or 0.6 to 1.2 mg.

OFFICIAL PREPARATIONS.—(i) *Injectio Physostigminæ Salicylatis* (*Inj. Physostig. Salicyl.*), See p. 46. **DOSE** as of Physostigmine salicylate by

subcutaneous injection. If the strength is not stated a solution containing 1/100 gr. in 15 min. or 0.6 mg. in 1 ml. is dispensed. (ii) *Lameilla Physostigminæ* (*Lamell. Physostig.*), See p. 48. Contains 1/1000 gr. (0.065 mg.) of physostigmine salicylate. (iii) *Oculentum Physostigminæ* (*Oculent. Physostig.*), (0.125%). See p. 51.

Pharmacology [and Therapeutics]

Physostigmine has *three* important *actions* :

(i) It excites the nerve-endings of both the **voluntary** and the **involuntary muscles**.

(ii) It excites the nerve-endings of the different **secretory glands**. This takes place with the usual therapeutic doses and more marked with poisonous doses.

(iii) Given in poisonous doses it paralyzes the **central nervous system**, especially the respiratory centre in the medulla so that death takes place from respiratory failure. The cardiac centre is also affected with such a dose and the heart stops in diastole.

MODE OF ACTION.—It has been found that physostigmine **inhibits choline-esterase** and retards rapid destruction of acetylcholine. It thus has *muscarine action* (on the heart, blood-vessels, unstriated muscles and glands) and some *nicotine action* (on the skeletal muscles and autonomic ganglia).

A minimal dose will simply inhibit the choline esterase and increase parasympathetic excitability. By increasing the dose, the saturation limit of the enzyme mechanism is reached and maximum inhibitory effect is produced : any dose beyond this, will cause the specific action of the alkaloid.

Further by increasing the **suprarenal secretion** (preservation of acetylcholine liberated by the splanchnic nerve impulses to adrenals) it may cause vascular side-effects.

So it may not always be possible to accurately predict the action : this may antagonize or even supercede the muscarine effect. But a *therapeutic dose* in a human being will have more obvious action on the pupil and the bowels and none on the voluntary muscles but one suffering from myasthenia gravis shows marked action in these muscles.

ACTION ON THE VOLUNTARY MUSCLES.—A therapeutic dose has no apparent action : a poisonous dose given to a rabbit causes fibrillary twitchings which start from the hind limbs and spread to the rest of body. The action is due to the excitation of the motor nerve-endings : these continue under chloroform anæsthesia but disappear if the nerves are paralysed by curare but are unaffected by atropine. These twitchings may be severe enough to cause convulsion. There is also probably some direct action on the muscles themselves. [It has recently been prescribed in **myasthenia gravis** with benefit (Walker, 1934). 1/64 to 1/32 gr. (1 to 2 mg.) is given hypodermically 2 or 3 times daily with atropine : the latter counteracts

disadvantageous actions of physostigmine on the glands and unstriated muscles.

ACTION ON THE INVOLUNTARY MUSCLES.—The most important action is on the *eye*, on the iris and the ciliary muscles. A $\frac{1}{2}$ to 1% solution or a lamella of the alkaloid applied to the conjunctiva, causes in half an hour, marked **contraction of the pupil**. This is due to excitation of the third nerve terminals in the iris by inactivating cholinesterase but no direct action on the circular muscles. It is, therefore, antagonistic to atropine which dilates the pupil by paralysing these muscles. Shortly after this, the ciliary muscles also contract adjusting the lens for near objects so that there is **loss of accommodation** for distant vision. The pupillary contraction lasts for 10 to 15 hours, but the loss of accommodation for 2 to 3 hours only. The **intraocular tension** is markedly reduced. This is due to drawing in of the iris and thus allowing a free passage to the intraocular fluid, also to some extent due to contraction of the intraocular blood vessels, lessening the secretion of fluid. [A $\frac{1}{2}$ to 1% solution^{416, 417} is applied to the eye to prevent adhesion or prolapse of the iris in case of an ulcer or a penetrating wound in the cornea. It is also used in glaucoma where the intra-ocular tension is high. These are the *only conditions in which physostigmine is used to any extent in practical medicine.*]

There is similar excitation of the muscles of the stomach, intestine, urinary bladder, gall-bladder, uterus and of the spleen. Thus, in bigger doses, physostigmine causes vomiting followed by watery evacuations: also pain in the abdomen and dyspnoea.

It causes constriction of the **bronchi**: the respiration becomes difficult and the symptoms may almost resemble bronchial asthma. There is often marked automatic movements of the other involuntary muscles also.

[Sometimes it is useful in atonic condition of the bowels and is either added to purgatives orally or is preferably given hypodermically especially in post-operative paresis in 1/100 gr. or 0.6 mg. dose but prostigmin and carbachol are more dependable and popular].

Further, it stimulates the **suprarenal medulla** (the nerve supply to the medulla is cholinergic). Adrenaline secreted may have either an *intensifying effect* as on the uterus and the heart or *inhibitory*, as on the intestinal movements: peristalsis may be lessened and heart rate increased for the time being.

CIRCULATION.—The heart is at first slightly slowed due to the excitation of the vagal endings and not to any direct

(416) B

Physostig. Salicyl. gr. 2

Sod. Metabisulph. gr. $\frac{1}{4}$

Inj. Sod. Chlor. fl. oz. 1.

To drop into the eye.

(417) B

Physostig. gr. 1

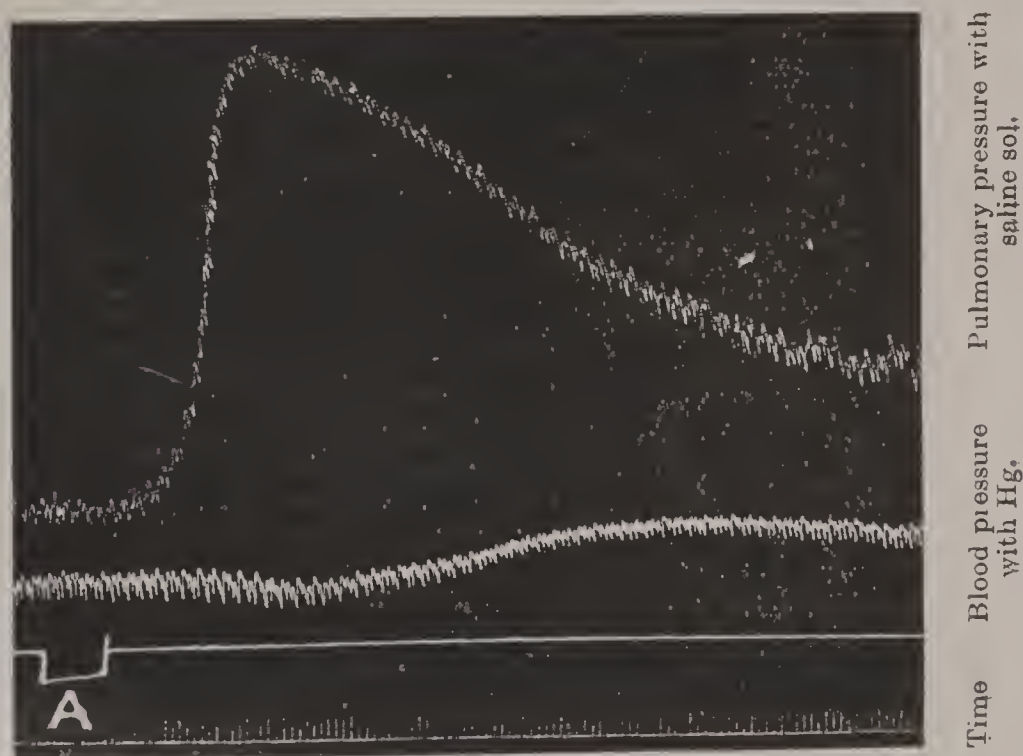
Hydrarg. Oxid. Flav. gr. 2

Paraff. Moll. Flav. oz. 1

Ung. For the eye

action on the heart muscle. But with a bigger dose the heart is even more slowed. The heart finally stops in diastole. In a frog, certain direct action on the muscle is also present increasing the force of contraction so that stimulation of the vagus fails to stop the heart.

The **blood pressure** rises partly due to constriction of the arterioles from excitation of the vaso-motor ganglia and partly also from direct action on the arterial muscles as the pulmonary blood vessels are also constricted which have no vaso-motor nervous control. This is further aided by strong contraction of the muscles of the abdominal viscera driving out blood from the mesenteric vessels. But towards the end, as the heart is very much slowed, the output is lessened and the blood pressure falls.



(Dixon)
Fig. 40.—At A a small injection of physostigmine was given into the femoral vein. Blood pressure rose, heart beat first quickened and then slowed. Pulmonary blood pressure also rose (constriction of the pulmonary vessels).

RESPIRATION.—In the beginning it is somewhat accelerated probably due to central excitation and to partial asphyxia caused by broncho-spasm. Afterwards, it becomes slow and feeble (medullary paralysis) and death follows from asphyxia.

SECRETORY GLANDS.—The typical action is shown on the salivary glands. The secretions are increased even with a dose not sufficient to affect the involuntary muscles, including the heart. The secretory nerve-endings are stimulated causing a

copious outpouring of saliva. But as after some time, the blood supply of these markedly diminishes from vaso-constriction, the secretion also diminishes.

The **sweat, pancreatic, mucous**, (both of the respiratory and of the alimentary tracts), **suprarenal** and the **lachrymal glands** also are affected in the same way. But secretions of milk, bile and urine are more or less unaffected.

CENTRAL NERVOUS SYSTEM.—In a case of poisoning, the motor *cortex* becomes **more excitable**: occasionally convulsions occur in a dog. This is followed by ascending **paralysis**; starting from the *spinal cord*, it extends to the *medulla*. After some preliminary acceleration, death follows from respiratory failure. The higher psychic centres are not affected.

PERIPHERAL NERVES.—In addition, physostigmine causes **fibrillary twitching** of the voluntary muscles: this is not stopped by dividing the nerves but is stopped by curare: on this atropine has no action. So on the voluntary muscles, physostigmine and curare are mutual antagonists and their site of action is identical. Acetylcholine also has similar action on the muscles and physostigmine action may really be due to acetylcholine.

EXCRETION.—It is mostly destroyed in the tissue and only a small portion is excreted in the urine unchanged.

SYMPTOMS OF POISONING are epigastric pain, vomiting, diarrhoea, salivation, contraction of the pupil, giddiness, muscular weakness, dyspnoea, perspiration, slow pulse and muscular twitchings with collapse.

Treatment.—The stomach is washed with 0.2% permanganate solution and atropine sulphate is given hypodermically: analeptics are required for respiratory failure.

NEOSTIGMINE, Prostigmin

1. NEOSTIGMINÆ METHYLSULPHAS (*Neostig. Methylsulph.*), $C_{13}H_{22}O_6N_2S$.

Neostigmine Methylsulphate is dimethylcarbamic ester of 3-hydroxyphenyltrimethyl-ammonium methylsulphate. Contains not less than 98% of $C_{13}H_{22}O_6N_2S$, dried at 100° for six hours.

A white, inodorous, crystalline powder with bitter taste. Soluble at 15.5° in 10 of water: less soluble in alcohol (90%).

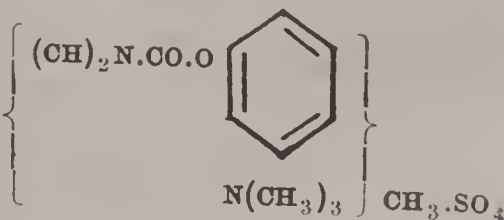
Dose, 1/120 to 1/30 grain or 0.5 to 2 mg. by subcutaneous or intramuscular injection.

Injectio Neostigminæ Methylsulphatis (*Inj. Neostig. Methylsulph.*), See p. 45.

Dose as of Neostigmine methylsulphate. If strength is not stated, 1/120 gr. in 15 min. or 0.5 mg. in 1 ml. is dispensed.

2. NEOSTIGMINÆ BROMIDUM (*Neostig. Bromid.*).

Neostigmine bromide, $C_{11}H_{14}O_3N_2Br$, is the dimethylcarbamic ester of 3-hydroxy-phenyl-trimethyl ammonium bromide. It contains not less than 93% of $C_{11}H_{14}O_3N_2Br$ dried at 100° for six hours.



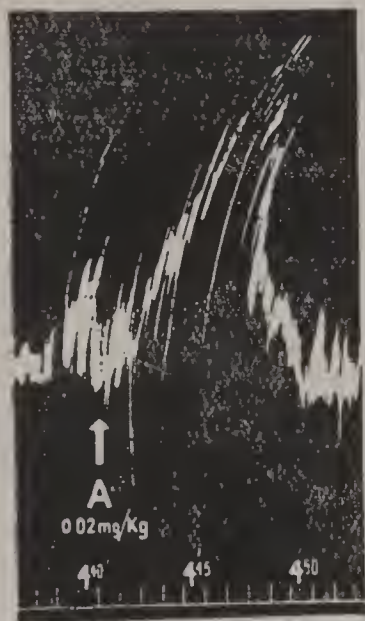
A white, inodorous, crystalline powder with bitter taste. Soluble at 15.5° in about 1 of water and in alcohol (90%).

Dose, $\frac{1}{6}$ to $\frac{1}{3}$ grain or 10 to 20 mg.

Pharmacology [and Therapeutics]

Neostigmine was first introduced into medicine as *Prostigmin* (Roche, 1931). Its action largely resembles the same of physostigmine and the mechanism is also probably the same.

It inhibits the activity of cholinesterase in the tissues and thereby prolongs the action of acetylcholine formed at the cholinergic nerve-endings. It has *nicotine-like action* on the voluntary muscles but less *muscarine action* on the eye, heart muscles and on the blood pressure. Further like physostigmine, given in large doses it depresses the skeletal muscles.



(Roche)

Fig. 41.—Increased intestinal peristalsis following intravenous injection of neostigmine.

In a human being, (a) unlike physostigmine, it does not cause much *miosis* and *spasm of accommodation* and has less effect on the *heart* and *blood pressure*. (b) But it has the same action on the *intestine*, *urinary bladder*, *skeletal muscles* and on the *skin blood vessels*. Further, neostigmine is a more stable preparation.

Neostigmine appears to have a *synergistic action* on mecholyl. If these are given one soon after the other, sweating, flushing, lacrymation : increased gastric secretion and increase of heart rate and blood pressure (rarely a fall) are more marked. These should be kept in mind in their therapeutic administration. Its action on the smooth muscles is *antagonised* by atropine and on the skeletal muscles by curare. (See p. 568).

The therapeutic effects are seen in 10 to 30 minutes after an injection of neostigmine methylsulphate or one to two hours after oral administration of neostigmine bromide.

INTESTINE and URINARY BLADDER.—Very striking results are produced in postoperative distention of the *intestine* also *urinary bladder atony* with retention of urine. As a *prophylactic*, $\frac{1}{4}$ mg. (half ampoule) of prostigmin is given hypodermically 24 hours before the operation and repeated every 4 to 6 hours up to the 2nd or 3rd postoperative day. If the *symptoms have already appeared*, 1 c.c. ($\frac{1}{2}$ mg.) is given subcutaneously every three hours along with a low enema : 4 to 5 injections are usually necessary.

In taking the **X-ray picture** of the intestine, 2 ampoules of prostigmin are injected on the night before and 2 more in the morning one hour before radiography. By dispelling gas from the intestine, a better view is obtained.

OTHER USES.—**Myasthenia gravis** is remarkably relieved (Mary Walker, 1935). In addition to its anti-cholinesterase properties, probably it has some *direct stimulant action* on the muscles (Comroe, 1946). The starting dose may be 0.5 mg. or 1 c.c. 3 to 4 times daily, increased if necessary. The objective signs as ptosis, difficulty in swallowing and facial movements and total muscular power remarkably improves. The effects are apparent in 5 minutes, maximum in 30 minutes and subsides in 3 to 5 hours. As the disease is chronic, the effects are kept up by oral administration of 15 mg. of neostigmine bromide 3 or 4 times daily. It may also be used in other chronic nerve diseases as spastic cerebral palsy. Simultaneous administration of atropine may be necessary to prevent the muscarine action.

Prostigmin is useful in **peripheral vascular disturbances** as Raynaud's syndrome, thrombo-angiitis obliterans, arteriosclerosis and acrocyanosis. By causing vaso-dilatation, peripheral circulation is re-established : may be used by injection or/and orally.

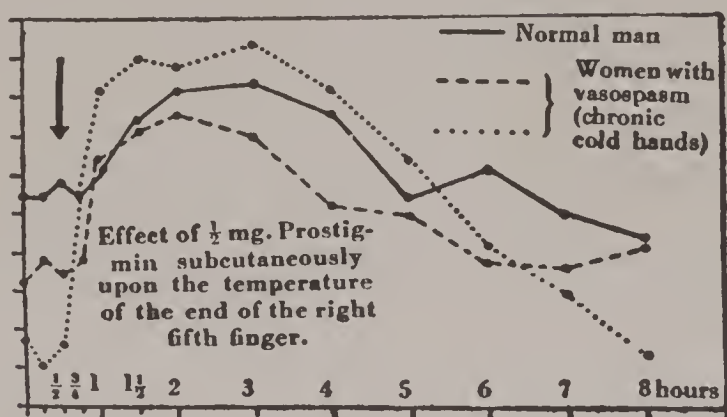


Fig. 42.—The peripheral vascular effects of prostigmin subcutaneously under different conditions. (Roche)

Neostigmine has been given in **supraventricular tachycardia** : 1 mg. of methylsulphate intramuscularly followed by 15 mg. of bromide orally 3 times daily may do.

OTORHINOLARYNGOLOGY.—Prostigmin has been found useful in the treatment of deafness, tinnitus aurium and Eustachian tube blocking : locally by spraying, in atrophic rhinitis.

Prostigmin is of some value in **glaucoma** and used as 3 to 5% drops.

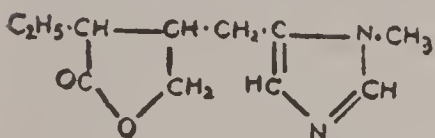
GYNÆCOLOGY.—In menstrual delay, 1 c.c. on 3 successive mornings or even 2 c.c. for 4 days, may bring in menstruation. If no menstruation follows, pregnancy may be diagnosed. Prostigmin will not interrupt pregnancy.

Available as *Prostigmin* ampoules 1·1 c.c. (0·5 mg.) and tablets 15 mg. each : also 3% eye drops and 1% ointment.

DI-ISOPROPYL-FLUOROPHOSPHONATE, *D.F.P.* has more intensive action than physostigmine and neostigmine : 0·05 to 0·1% solution in arachis oil as *eye drop* in glaucoma : it is of some value in 0·1% solution in 2 c.c. ampoule in myasthenia gravis and paralytic ileus.

PILOCARPINE

PILOCARPINÆ NITRAS (*Pilocarp. Nit.*), Pilocarpine Nitrate,
 $C_{11}H_{16}O_2N_2HNO_3$.



It is nitrate of an alkaloid pilocarpine, obtained from *Jaborandi* leaves *Pilocarpus microphyllus* and other varieties of *Pilocarpus*.

Colourless crystals or white crystalline powder. Soluble in about 8 parts of water.

Dose, 1/20 to 1/5 grain or 3 to 12 mg.

Pharmacology [and Therapeutics]

Pilocarpine acts much like physostigmine except that it has (a) *no marked action* on the central nervous system, none on the voluntary muscles and less pronounced action on the blood vessels. It *acts directly* on the post-ganglionic nerve-endings of the parasympathetic system and not through activation of acetylcholine. It thus acts like muscarine and the actions are more directly antagonistic to those of atropine. (b) It has an *excitant action* on *glands* and on *involuntary muscles*.

(i) ON NERVE-ENDINGS AT THE MYO-NEURAL JUNCTION IN DIFFERENT GLANDS.—The secretion of the salivary, sweat, gastric, pancreatic and intestinal glands : of the mucous glands in the mouth, nose and respiratory tract : of ceruminous and lachrymal glands and also of the suprarenal glands are increased. Those of milk, bile and urine are not definitely affected. This increased secretion affects both the solid and the liquid portions. This action is mostly direct on the glands and to some extent by increasing the blood flow.

The secretion of sweat is so profuse that pilocarpine is the most **powerful diaphoretic** and occasionally used by subcutaneous injection of 1/5 grain or less in general anasarca. [This was one time prescribed in œdema of kidney disease with deficient urinary secretion. A fair amount of urea, salts and water passed out by the skin which, to some extent, relieved the renal deficiency especially when uræmia was threatening. But this was followed by general depression which did more harm than good]. Its power of increasing other secretions is seldom of any practical value. These effects are inhibited by atropine.

(ii) ON THE PARASYMPATHETIC NERVE-ENDINGS AT THE MYO-NEURAL JUNCTION.—All involuntary muscles are affected. Thus peristalsis is increased and also the glandular secretions of

the alimentary tract causing vomiting, intestinal colic and profuse diarrhoea. This action is antagonised by atropine.

The same action on the **bronchioles** leads to their spasmodic contraction which may be severe enough to resemble bronchial asthma. Circulation through the lungs is diminished and in fatal poisoning, increased bronchiolar secretions combined with venous stasis, causes pulmonary oedema.

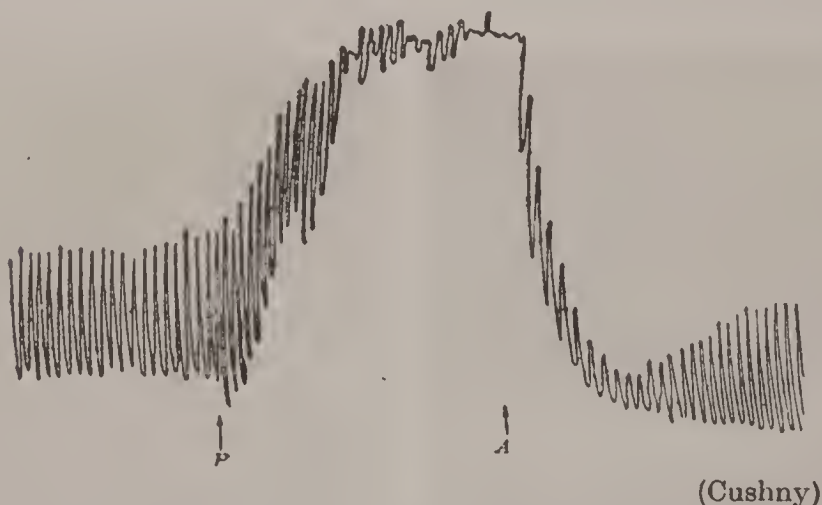


Fig. 43.—The antagonism between pilocarpine and atropine on the intestine. Pilocarpine was injected at P resulting in marked tetanic spasm which was relieved by atropine, injected at A. (Cushny)

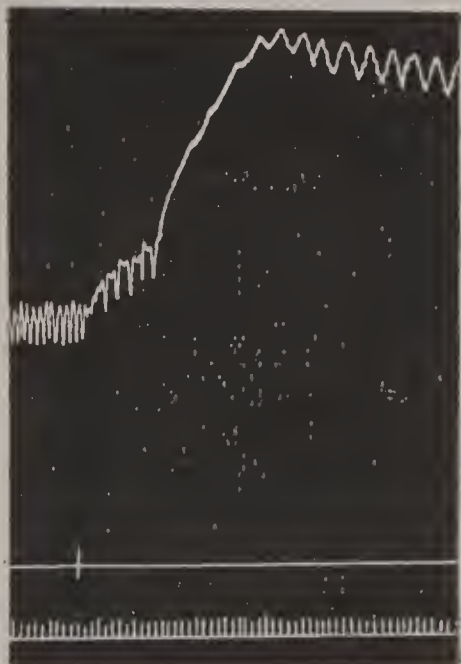
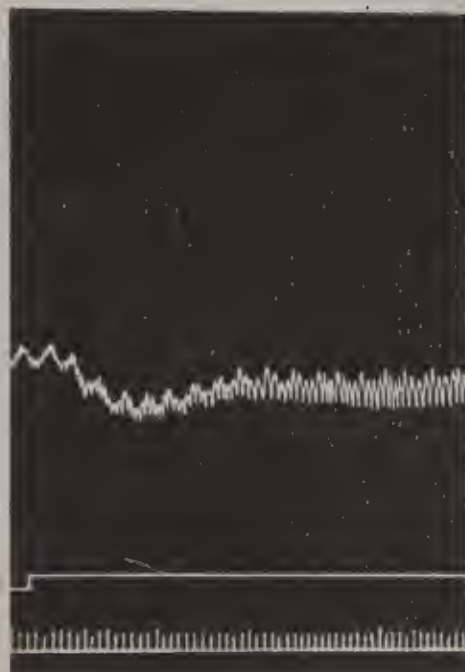
By its action on the third nerve-endings, the **pupil** is contracted which disappears on applying atropine and the power of **accommodation** is lost from contraction of the ciliary muscles, the lens being adapted to near vision. **Intraocular tension** is markedly reduced, although there may be a slight preliminary rise. [It is occasionally used as a substitute for physostigmine in 2% solution].

The **uterus** also contracts and if gravid, there may be abortion. **Urinary bladder** is frequently evacuated with straining.

But these actions are less marked than those of physostigmine.

(iii) **THE CIRCULATION.**—Here the complete muscarine action is not produced. The action varies with the species of the animal acted on and the dose. Applied *locally* on the heart of a dog it **slows the rate** and finally causes diastolic stoppage by stimulation of the vagal endings. Given *intravenously* to a cat or a rabbit, the heart is slowed, the arterioles dilate and the blood pressure falls. Soon the vagal endings are depressed and the former heart rhythm is restored but as the heart muscles also are depressed, the heart becomes slow again and feeble. In man and dog also the vagal stimulation causes slowing but this may sometimes be absent; the pulse is quickened and the blood pressure rises.

The **blood vessels**, especially of the limbs and of the splanchnic area are constricted due to increased suprarenal secretion but those of the head and neck are moderately dilated showing cholinergic action. This combined with some quickening of the heart beat, slightly raises the blood pressure. Given in a bigger dose, it acts directly on the cardiac muscles as depressant and the circulation is made feebler ; the blood vessels dilate and the blood pressure falls.



Pilocarpine

Atropine (Dixon)

Fig. 44-45.—At the first mark, pilocarpine 1 c.c. 0.3% is injected into jugular vein. The heart is slowed, blood pressure slightly falls and then slightly rises (vaso constriction). At the second mark 1 c.c. of 0.1% atropine is given and blood pressure markedly rises.

Temperature in the beginning is slightly raised but increased perspiration soon brings it down.

There is a certain amount of **leucocytosis** probably due to contraction of the unstriped muscle-fibres of the spleen and of the lymphatic glands which presses out the leucocytes. **Blood sugar** tends to go up in a rat.

(iv) **OTHER ACTIONS.**—Pilocarpine promotes the growth of hair^{418, 419} probably by stimulating the skin glands also

(418) R

Quinin. Hydrochlor.

Pilocarp. Nit. aa. gr. 10

Liq. Epispast. min. 15

Aq. Rosmarin. ad. fl. oz. 4

To be rubbed on the roots of the hair daily.

(419) R

Pilocarp. Nit. gr. 2

Quinin. Hydrochlor. gr. 10

Liq. Epispast. min. 2

Glycer. min. 120

Aq. Rosæ ad. fl. oz. 1

Hair lotion.

causing increased vascularity [and is therefore included in many hair toilets.

Pilocarpine is sometimes used to relieve itching as from jaundice : also used symptomatically for labyrinthine disorders.

The quantity of **urine** passed gets less on account of much loss of fluid through sweat, vomit and stool.

It has no marked action on the **central nervous system**. Given intravenously, it may cause some convulsive movements and muscular weakness. These may however be due to circulatory failure from depression.

SUMMARY.—Anticholinesterase drugs are choline group (acetyl choline bromide, carbachol and mecholyl), physostigmine, neostigmine and pilocarpine. Their general actions are (i) *parasympathetic stimulation* causing (a) contraction of the unstriated muscle fibres especially of the intestine and urinary bladder and iris and ciliary muscles, (b) increasing the secretion of glands and (c) dilatation of the blood vessels : inactivated by atropine. (ii) Stimulating action on the motor end-plates of the *skeletal muscles* : inactivated by curarine.

The **drugs of choice** are (a) for stimulating the *unstriated muscle fibres*, choline group and neostigmine : (b) on the *eye*, physostigmine and pilocarpine : (c) on the *cardiovascular system*, choline group and neostigmine : (d) for increasing *glandular secretions*, pilocarpine and (e) for stimulating the *skeletal muscles*, neostigmine and to some extent, physostigmine.

ARECHOLINE (Not official), alkaloids of arecanut, is cholinergic, increasing the tone and automatic movements of most of the *plain muscles* of the body as of the alimentary canal, uterus, bronchioles and the pupil : slowing the *heart rate* and acting as a powerful *sialogogue*.

COLCHICUM

1. COLCHICI CORMUS (*Colch. Corm.*), Colchicum corm.

Fresh corm or the same with coats taken out of *Colchicum autumnale*, collected early in summer sliced transversely and dried at a temperature not exceeding 65° : inodorous with bitter acrid taste. A dried corm should contain not less than 0.25% of Colchicine.

A *dried slice* is 1 to 3 × 1 to 2 cm. and thick, firm and whitish but yellowish at the circumference and reniform in outline owing to indentation on one side. Taste is bitter and acrid. It contains an active alkaloid *colchicine* and also a certain amount of veratrine, starch, sugar, gum and a fixed oil.

It is mainly obtained from Great Britain. The Indian variety, *Colchicum luteum* or *Surinjan*, that grows in the Western Himalayas, Kashmere and Chamba, contains colchicine and is in the IND. PHARM. LIST, an effective substitute.

COLCHICI CORMI PULVIS (*Colch. Corm. Pulv.*), is a finely made light grey powder of colchicum corm.

INCOMPATIBLES.—All astringent preparations, liquors of iodine and tincture of guaiacum.

2. COLCHICI SEMEN (*Colch. Sem.*), Colchicum seed.

The dried ripe seeds of the above, contain a greater proportion of the alkaloid than the corm and also a volatile oil. These must contain not less than 0.3% of colchicine

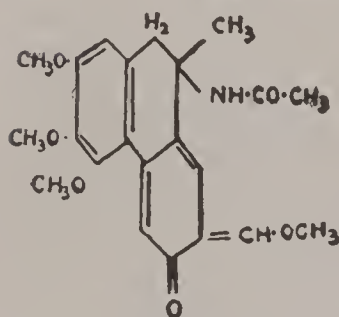
These are ovoid or irregularly globular 1/12" to 1/8" (2 to 3 mm.) in diameter, somewhat pointed, reddish brown in colour : occasionally paler, minutely pitted, hard and rough ; internally whitish or light brown : inodorous with a bitter acrid taste.

COLCHICI SEMINIS PULVIS (*Colch. Sem. Pulv.*) is a brown powder of *Colchicum* seeds.

OFFICIAL PREPARATIONS.—(i) **Extractum Colchici Liquidum** (*Ext. Colch. Liq.*), See p. 39. Contains 0.3% w/v or in 5 minims 1/70 grain of colchicine. (ii) **Tinctura Colchici** (*Tinct. Colch.*), See p. 59. It contains in 15 min. 1/200 gr. of colchicine (0.03%). Dose, 5 to 15 minims or 0.3 to 1 ml.

These are in the **IND. PHARM. LIST** also.

3. COLCHICINA (*Colchicin.*), $C_{22}H_{25}O_6N$.



Colchicine

cine. Strength 1%. Dose, $\frac{1}{6}$ to $\frac{1}{2}$ gr. or 10 to 30 mg.

VINUM COLCHICI (Not official).—*Colchicum* corm 200, macerated with sherry 100.

Dose, 10 to 30 minims or 0.6 to 2 ml.

Colchicine is an alkaloid obtained from the corm and seeds of *Colchicum autumnale*. Pale yellow crystals, amorphous scales or powder, darkens on exposure to light: inodorous and bitter. Readily soluble in water, alcohol 95% and chloroform: soluble in 160 of solvent ether.

Dose, 1/120 to 1/60 grain or 0.5 to 1 mg. Total dose, 1/30 to $\frac{1}{2}$ gr. or 2 to 8 mg.

OFFICIAL PREPARATION.—**Extractum Colchici Siccum** (*Ext. Colch. Sicc.*), See p. 39. Containing in 1 gr. about 1/100 gr. of colchicine.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, it is an **irritant** causing redness and pain at the site. It acts more powerfully on the mucous membrane.

Colchicine ointment (0.05 of colchicine in 100 g. of lanoline), 2 c.c. applied morning and evening for a month has been found useful in vulval papillomata (Bourg and Dustin, 1945).

TAKEN BY MOUTH in a big dose, it causes **vomiting** and **diarrhoea** by increasing the contractions of both stomach and intestine. This is due to excitation of the peripheral vagal endings as it disappears after atropine. It causes, in addition, marked irritation of the mucous membranes. In the same way, the muscular contractions of the bronchioles, uterus and the spleen are definitely increased. But unlike pilocarpine, it has very little action on the nerve terminals of the heart and of the glands.

It has a slow toxic action on the *central nervous system*. It causes slow motor and sensory paralysis and death ultimately follows from the failure of respiratory and vasomotor centres.

It has a remarkable action on the **leucocytes**. At first, for a period of an hour or so, there is leucopenia followed by definite leucocytosis which mostly involves the polymorphonuclears. This action is not probably specific and is the outcome of gastro-intestinal irritation.

Circulation is almost unaffected but with a poisonous dose, this is depressed causing small rapid pulse : this may be partly due to severe gastro-enteritis which is associated.

Respiration in the beginning is made slow and of greater amplitude but afterwards feeble, death following from respiratory failure.

Its action on the *kidneys* is variable. It may cause anuria for hours or moderate diuresis and sometimes hæmaturia. There is no evident increase of the elimination of uric acid.

Recently colchicine has been found to greatly increase mitosis of cells in both normal and malignant tissues. But no therapeutic possibility is yet in sight.

This has a great reputation as a specific remedy for gout in its acute stage^{420, 423} relieving promptly the painful swelling of the joint and its therapeutic use is practically limited to this condition. Colchicine 0.5 mg. (1/120 gr.) tablets, liquid extract (2 to 5 minims), dry extract 15 mg (gr. $\frac{1}{4}$) or tincture of colchicum 15 to 30 minims (1 to 2 ml.) is given every 4 hours or more frequently in a severe case in the acute stage, but it is not known how it acts. Gout is associated with an increase of uric acid in the blood which is deposited in the affected joints as an insoluble urate. Although colchicum is slightly diuretic, it does not very much increase the excretion of uric acid : other diuretics, even more powerful than this, have not the power of relieving pain of gout as promptly.

During its administration, care should be taken to avoid *gastro-intestinal irritation* and also to prevent its accumulation by combining it with a mild purgative. It is of less value in other gouty manifestations as dyspepsia, asthma, eczema, chronic joint and nerve affections.

SUMMARY.—Colchicine, somewhat like Pilocarpine, causes excitation of the plain muscles and to a less extent of the glands and in addition, in bigger doses, acute gastro-enteritis and renal congestion : but it has specific action in acute gout and this is its only therapeutic use.

B. DRUGS DEPRESSING THE PARASYMPATHETIC NERVE-ENDINGS

These are drugs of the *atropine group*, obtained from,

(i) **Belladonna Herb and roots** containing *hyoscyamine* and *atropine* : the latter is in greater proportion.

(420) R

Tinct. Colch. min. 15

Pot. Bicarb.

Mag. Carb. aa. gr. 15

Aq. Menth, Pip. ad. fl. oz. 1

Every 4 hours for gout.

(421) R

Tinct. Colch. min. 10

Mist. Alba oz. 1 (Guy's)

Every 3 to 4 hours for gout.

(422) R

Tinct. Colch. min. 10

Pot. Cit. gr. 20

Mag. Sulph. gr. 60

Inf. Buchu. Rec. ad. fl. oz. 1

(Middlesex)

Every 3 hours for gout.

(423) R

Ext. Colch. Sicc. gr. $\frac{1}{2}$

Ext. Casc. Sagr.

Aloes aa. gr. 1

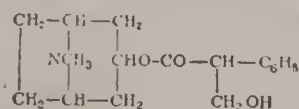
Ext. Bellad. Sicc. gr. $\frac{1}{6}$

Pil. For chronic gout.

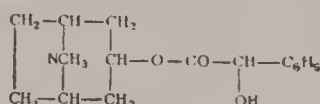
(ii) **Stramonium leaves and seeds** also containing *hyoscyamine* and *atropine* and, in addition, a third alkaloid, *hyoscyne* or *scopolamine*.

(iii) **Hyoscyamus leaves** containing chiefly *hyoscyamine* and small quantities of *atropine* and *hyoscyne*.

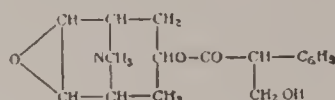
These three alkaloids are closely related to each other. *Atropine*, $C_{17}H_{23}O_3N$, contains active *laevohyoscyamine* and less active *dextrohyoscyamine* in equal portion. In a plant it exists in these forms and not unlikely that *atropine* is formed during extraction. *Hyoscyne*, $C_{17}H_{21}O_4N$, is also very closely allied.



Atropine



Homatropine



Hyoscyne

These are decomposed into *tropine*. Artificial tropines have also been prepared. The only successful one therapeutically so far is ester of tropine and mandelic acid, called *homatropine*.

BELLADONNA, Deadly Nightshade

A. **BELLADONNÆ HERBA** (*Bellad. Herb.*), *Belladonnæ Folium*, *Belladonna Leaf*.

Belladonna Herb consists of leaves or leaves and other aerial parts of *Atropa Belladonnæ* Linn, or of *Atropa Acuminata* Royle ex Lindley or a mixture of both species collected from flowering plants and dried, containing not less than 0.3% of total alkaloids, calculated as *hyoscyamine*.

The *leaves* are somewhat crumpled and twisted, partly matted or in fragments: these alternate often in pairs, big and small: green or greenish brown, 2 to 10 inches (5 to 25 cm.) long and 1 to 5 inches (2.5 to 12 cm.) wide: ovatelanceolate or broadly ovate with a pointed apex: a drooping *flower* on a short pedicel or an axillary shoot: *stem* more or less hollow and flattened: *fruit* immature subglobular, green or brown with many reniform seeds.

Slight odour and slightly bitter and acrid taste.

BELLADONNÆ HERBÆ PULVIS (*Bellad. Herb. Pulv.*), powdered *belladonna herb* is greenish in colour.

OFFICIAL PREPARATIONS.—(i) **Belladonna Præparata** (*Bellad. Præp.*), See p. 52. It is *standardised* to contain 0.3% of the alkaloids calculated as *hyoscyamine*: 3 grains contain 1/100 gr. of the alkaloids. Dose, $\frac{1}{2}$ to 3 grains or 30 to 200 mg. (ii) **Extractum Belladonnæ Siccum** (*Ext. Bellad. Sicc.*), See p. 38. It is *standardised* to contain 1% of total alkaloids calculated as *hyoscyamine*. In 1 gr. about 1/100 gr. of the alkaloids of *belladonna herb*. Dose, $\frac{1}{2}$ to 1 grain or 15 to 60 mg. (iii) **Tinctura Belladonnæ** (*Tinct. Bellad.*), See p. 59. It is *standardised* to contain about 0.03% of total alkaloids calculated as *hyoscyamine*. Dose, 5 to 15 minims or 0.3 to 1 ml.

B. **BELLADONNÆ RADIX** (*Bellad. Rad.*), *Belladonna Roots*.

These are the dried roots of *Atropa Belladonna* Linn. or *Atropa Acuminata* Royle ex Lindley or a mixture of both.

Almost cylindrical, entire or longitudinally split, sparingly branched about $\frac{1}{2}$ to 1" (4 cm.) in diameter: outside, pale greyish-brown, finely wrinkled longitudinally: inside, whitish to brownish: sometimes crowned by the root stock (*A. Belladonna*).

Cylindrical pieces, thinner (0.5 to 3 cm. in diameter) and occasionally branched: thicker at the summit, 4 to 12 aerial stems at the base:

slightly contorted, longitudinally wrinkled and pale brownish-grey in colour, (*A. Acuminata*).

It is *standardised* to contain not less than 0·4% of the alkaloids of the Belladonna root calculated as hyoscyamine. In India, it grows in Kashmere State and in Simla.

BELLADONNÆ RADICIS PULVIS (*Bellad. Rad. Pulv.*), powdered belladonna root is grey to light brown in colour.

OFFICIAL PREPARATIONS.—(i) **Extractum Belladonnæ Liquidum** (*Ext. Bellad. Liq.*), See p. 39. It is *standardised* to contain 0·75% of the alkaloids calculated as hyoscyamine : about 1/150 gr. in 1 min. (ii) **Linimentum Belladonnæ** (*Lin. Bellad.*), See p. 49. *Standardised* to contain 0·375% of alkaloid, calculated as hyoscyamine and camphor 5%. (iii) **Suppositorium Belladonnæ** (*Supp. Bellad.*), See p. 54. Each is *standardised* to contain about 1/60 grain or 1 mg. of the total alkaloids.

1. ATROPINA (*Atrop.*), Atropine, Atropia, $C_{17}H_{23}O_3N$.

The alkaloid *dl-hyoscyamine*, is obtained from *Atropa Belladonna*, *Hyoscyamus Muticus* and other plants of the same family.

Colourless, inodorous crystals, soluble at 15·5° 1 in 500 of water but freely so in alcohol (90%) and in chloroform. Soluble at 20° in 60 of solvent ether.

INCOMPATIBLES.—The usual alkaloidal precipitants. Caustic alkalies decompose it.

UNGUENTUM ATROPINÆ (Not official).—Atropine 2, oleic acid 8 and lard or suet 90, (1 in 10 or 2%).

2. ATROPINÆ SULPHAS (*Atrop. Sulph.*), Atropine sulphate ($C_{17}H_{23}O_3N$)₂H₂SO₄H₂O.

This is a nearly colourless, inodorous crystalline substance, the sulphate of the alkaloid, atropine, soluble at 15·5° in less than 1 of water and in 4 of alcohol 90%.

Dose, 1/240 to 1/60 grain or 0·25 to 1 mg.

OFFICIAL PREPARATIONS.—(i) **Injectio Atropinæ Sulphatis** (*Inj. Atrop. Sulph.*), See p. 42. If strength is not stated, it should contain 1/100 gr. in 15 min. or 0·6 mg. in 1 ml. Dose as of Atropine sulphate. (ii) **Injectio Morphinæ et Atropinæ** (*Inj. Morph. et Atrop.*), See p. 44. Dose, 8 to 15 min. or 0·5 to 1 ml. Each ml. contains 1/100 gr. (0·6 mg.) of atropine sulphate and 1/6 gr. (10 mg.) of morphine sulphate. (iii) **Lamellæ Atropinæ** (*Lamell. Atrop.*), A disc contains 1/50 grain (1·3 mg.) of a basis made of gelatin and glycerin and 1/5000 gr. (0·013 mg.) of atropine sulphate. (iv) **Oculentum Atropinæ** (*Oculent. Atrop.*), See p. 51. (0·25%). (v) **Oculentum Atropinæ cum Hydrargyri Oxido** (*Oculent. Atrop. cum Hydrargy. Oxid.*), See p. 51. (vi) **Tabellæ Atropinæ Sulphatis** (*Tab. Atrop. Sulph.*), See p. 56. Strength, 89·5 to 112·5% of atropine. Dose, Same as of atropine sulphate : each tablet if not otherwise stated, should be of 1/100 grain.

3. HOMATROPINÆ HYDROBROMIDUM (*Homatrop. Hydrobrom.*), Hydrobromide of Homatropine, $C_{16}H_{21}O_3N$, HBr.

A white crystalline powder, being the hydrobromide of an alkaloid, homatropine, prepared from tropine and mandelic acid. Soluble at 15·5° in 6 of water and in 18 of alcohol 90%. It contains between 76 to 77·5% of the alkaloid.

Lamellæ Homatropinæ (*Lamell. Homatrop.*), A disc contains 1/100 gr. (0·65 mg.) of homatropine hydrobromide, made up with gelatin and glycerin 1/32 gr. (2·1 mg.).

Pharmacology [and Therapeutics]

The actions of the Belladonna preparations are mostly due to atropine.

Atropine

Atropine has got *three definite systemic actions*,—

- (i) The initial excitation of the **central nervous system**, especially of the *motor areas* followed by depression especially if the dose is increased.
- (ii) Paralysis of the parasympathetic nerve-endings in different **involuntary muscles**; including those of the heart and the eyes.
- (iii) Paralysis of the autonomic nerve-endings in different **secretory glands** also of the **sensory nerve endings**.

The last two actions of atropine are due to its *inhibiting* the muscarine-like effects of acetylcholine on the tissues although acetylcholine is liberated in the normal way.

APPLIED EXTERNALLY to the skin, Atropine **depresses** the terminations of the **sensory nerves** and **relieves pain**^{424, 425}, but such an effect is not produced unless it is rubbed into the skin with a substance like alcohol, glycerin or fat which favours its absorption but this action does not follow its internal administration. [Belladonna preparations are often applied in the form of paint, plaster or liniment to many superficial inflammatory conditions].

TAKEN INTERNALLY, either by the mouth or by hypodermic injection, atropine shows its specific action.

(1) **CENTRAL NERVOUS SYSTEM.**—The initial **stimulation** of the motor portions of the *brain* and the *medulla* is followed by their **depression**.

(a) A therapeutic dose causes moderate **medullary stimulation** only : the breathing becomes quicker and deeper and the blood pressure rises. (b) A dose nearly toxic, causes **cerebral stimulation**. At first a cheerful condition ensues with a lively flow of ideas, talkativeness and desire for movements : hallucinations of sight and hearing and delirium follow which may be either of a peaceful and happy nature or one of violence and rage. (c) On the **basal ganglia** it has a sedative action lessening the rigidity and tremor of parkinsonism. [Atropine is given hypodermically in narcotic poisoning especially by opium to stimulate the respiratory centre^{426, 427}. For parkinsonism, hyoscine and stramonium are more frequently used]. (d) If the

(424) ℞
Lin. Aconit.
Lin. Bellad.
Lin. Chlorof. aa. fl. oz. 1
A.B.C. Liniment.

(425) ℞
Ichthyol min. 60
Ext. Bellad. Sicc. gr. 8
Glycer. ad. fl. oz. 1
To apply over an inflamed joint or gland.

(426) ℞
Atrop. Sulph gr. 1/60
Strych. Sulph. gr. 1/60
Aq. pro Inj. min. 15
Hypodermically, in sudden cardiac or respiratory failure.

(427) ℞
Atrop. Sulph. gr. 1/60
Inj. Leptazol. min. 15
Hypodermically, in cardiac or respiratory failure.

dose is large, the motor cells of the spinal cord are also excited resulting in strychnine-like convulsions. All these are sooner or later, followed by depression and tendency to drowsiness and sleep. (e) After a very large dose, **coma** finally supervenes. The temperature falls, the pulse becomes feeble, irregular and very frequent. The respiratory centre is also depressed: the breathing is quickened and often interrupted by convulsive movements. Finally it becomes slow and shallow and death follows from asphyxia.

Unlike alcohol *atropine causes real stimulation* as shown by (i) stimulation of the psychic centre with a small dose; (ii) increased electrical and reflex excitability of the motor cells and (iii) excitation of the medullary centres (respiratory and cardiac).

Thus of the three excitants of the central nervous system, caffeine, atropine and strychnine, the first acts mostly on the highest psychic centre and the last, on the medulla and spinal cord: the second has an intermediate type of action, being most marked on the cranial motor centres and consequently these in atropine poisoning have an uncontrollable activity.

(2) PARASYMPATHETIC NERVE-ENDINGS.—The postganglionic fibres in various involuntary muscles and the secretory glands either at the receptor between the nerve-endings and the actual contractile substance of the muscles at the myoneural junction, or in the secretory cells of the various glands are paralysed: this is an action opposite to that of the muscarine group. (See p. 588). Briefly, it paralyses all nerve-endings having "cholinergic" fibres.

Certain parasympathetic activities as of vaso-dilator fibres of chorda tympani, nervi erigentes and the posterior nerve roots, cholinergic nerves to the uterus and motor vagus supplying the intestine are not paralysed.

(i) THE PLAIN MUSCLE-FIBRES.—By paralysing their peripheral nerve endings, the **contractility** of these muscles is **diminished**, causing relaxation especially if these are already in spasmodic condition.

(a) *Eyes*.—Atropine administered in a big dose internally or better a few drops of 1% atropine solution, and even such a weak solution as 1 in 10,000, applied for some time on the eye, cause marked **dilatation** of the **pupil**^{428, 430} by paralysing the third nerve endings at the myoneural junction which control the circular muscle fibres of the iris. This dilatation is due to the unopposed action of the radial fibres which are supplied by the cervical sympathetics. This is nearly complete in one hour

(428) B

Atrop. Sulph. gr. 4

Aq. Steril. ad. fl. oz. 1

Lotion: For dilating the pupil.

(429) B

Atrop. Sulph. gr. 2

Cocain. Hydrochlor. gr. 4

Aq. Steril. ad. fl. oz. 1

Lotion: For corneal ulcer

(430) B

Atrop. gr. 2

Cocain. gr. 4

Paraff. Moll. Alb. oz.

Ung. For the eye.

and persists for ten to fourteen days. But there is no paralysis of the muscles as they react to direct electrical stimulation. Neither the nerve is affected because atropine dilates the pupil of a recently excised eye. Moreover this dilatation is not maximum as further dilatation is possible by stimulating the sympathetics which control the radial fibres.

Belladonna in Italian means a fair lady : dilatation of the pupil was thought to improve the appearance and this plant was one time used in fashionable circle for this purpose.

That the action is *peripheral* is made out by (a) applying a minute crystal of the drug to one side of the cornea when only that portion of the pupil dilates : (b) after degeneration of the third nerve, atropine is capable of antagonizing the action of pilocarpine.

It also paralyses the ciliary muscles causing loss of **accommodation** especially for near vision by acting on the third nerve-endings and 1% solution of atropine is usually used. This takes more time than the dilatation of the pupil, but disappears earlier by about 4 to 7 days. This speciality differentiates belladonna group of drugs from sympathomimetic mydriatics (adrenaline, ephedrine or cocaine) which do not act on accommodation.

The **intra-ocular tension** is almost unaffected in a normal eye, but raised if it is already above normal. This is due to the dilated pupil obstructing the lymph flow. This makes it unsuitable for use in glaucoma where the tension is raised. Atropine is used as eye-drop in iritis and ulcer of the cornea to prevent adhesion of the iris.

Watery solution of the alkaloidal salt, oily solution of the alkaloid (usually 1%), oculenta or eye disc may be used.

(b) *Heart*.—Given in a small dose, as 0.5 to 1 mg. or 1/120 to 1/60 gr., owing to the initial stimulation of the vagal centre, there is slight slowing of the heart rate but this is seldom obvious. Given in a bigger dose as 2 mg. (1/30 gr.), the vagal endings are blocked and the heart action is **quickened** with increased force. The heart muscle however, is not directly affected : simply the inhibitory vagal influence is lost. Consequently, after a temporary fall, the **blood pressure slightly rises**. This is partly due to increased cardiac output and partly to medullary stimulation. These are not sufficiently evident in very young or old people, but in an adult with well-developed and active vagal system, are marked. In a normal animal, a moderate dose does not act on the **blood vessels**. But if dilated by acetylcholine, this effect is immediately counteracted by atropine. With a bigger dose it dilates the skin vessels especially of the head and neck by acting on the vaso-dilator centre, weakens the contraction of the heart muscles, increases the frequency of the heart beat and lowers the blood-pressure. Owing to the peripheral vaso-dilatation, the skin is flushed and in a susceptible person, a distinct rash may appear, resembling minute

mosquito-bites. [Atropine is given in *bradycardia* especially of heart block and of muscarine and pilocarpine poisoning. It is also useful as *pre-anæsthetic medication*, given preliminary to administration of a general anæsthetic. See p. 464].

(c) *Œsophageal muscles* are relaxed ; this along with lessening of secretion causes difficulty in swallowing.

In rabbits *œsophageal muscles* are striated and in cats the upper part striated and the lower part unstriated. Atropine paralyses through vagus the unstriated portion and curare, the striated portion.

(d) *Stomach and Intestine*.—With a therapeutic dose, main action of atropine is **sedation** to the peripheral nerve endings of the vagus without interrupting the path of the normal nervous impulses. If for any excessive local irritation, there is either violent movement or spasmodic contraction of any part of the intestine, atropine diminishes this excessive vagal tone and, by relaxing the plain muscle fibres, makes the contractions normal⁴³¹. [It is therefore frequently used for many kinds of *colic*⁴³² and is combined with strong purgatives to lessen their griping action⁴³³⁻⁴³⁴]. For this purpose, hyoscyamus is more popular than belladonna.

In the same way, hyperperistalsis caused by pilocarpine is antagonised by atropine (p. 599).

A large dose given in experimental condition to an animal may increase peristalsis probably from its action on the Auerbachs' plexus (Magnus) : vomiting and purging may therefore be occasionally seen in a case of poisoning.

(e) *Other plain muscles*.—On them also the same sedative action takes place. The **muscle fibres** of uterus, spleen, urinary and biliary passages are relaxed and this relieves local colicky conditions.

Atropine sometimes relieves *nocturnal enuresis* by depressing the detrusor muscles of the bladder.

(f) *Bronchial muscles*.—Atropine paralyses the vagal endings in the bronchial muscles and so these **are relaxed** by the unopposed action of the sympathetics. [It is frequently given hypodermically with adrenaline or ephedrine hydrochloride solution in bronchial asthma, a condition of spasm of the bronchioles]. For oral administration, stramonium is more

(431) R
Morph. Hydrochlor. gr. $\frac{1}{4}$
Supp. Bellad. gr. 15
For painful conditions in the rectum and prostate.

(432) R
Pot. Brom. gr. 15
Tinct. Bellad. min. 10
Sp. Æther. Co. min. 20
Aq. Aneth. ad. fl. oz. 1
For colicky condition.

(433) R
Ext. Casc. Sagr. Sicc. gr. 2
Ext. Bellad. Sicc.
Ext. Nuc. Vom. Sicc. aa. gr. $\frac{1}{4}$
Ext. Gent. q.s.
Pil. For habitual constipation.
(434) R
Ext. Colocynch. Co. gr. 3
Ext. Bellad. Sicc.
Ext. Nuc. Vom. Sicc. aa. gr. $\frac{1}{4}$
Ext. Gent. q.s.
Pil. For obstinate constipation.

popular than belladonna¹³⁵. It is also useful in whooping cough¹³⁶].

It is well to remember here that the bronchial secretion is diminished.

(ii) By its paralysing action ON THE NERVE-ENDING ON THE SECRETORY GLANDS, it stops all secretions. But this is not by any inhibitory action on the glandular cells themselves because secretion follows on their direct electrical stimulation.

(a) *Sweat*.—Taken internally orally or by injection, it stops the secretion of sweat¹³⁷, and the skin becomes dry: direct stimulation of the secretory nerves concerned produces no results. Therapeutically, atropine it is often used to stop excessive perspiration.

The skin glands, although supplied by the sympathetic nerves are cholinergic in function.

(b) *Salivary secretion*.—The mouth and the throat become dry causing difficulty in swallowing and articulation (paralysis of the chorda tympani endings, proved by direct electrical stimulation of the nerve).

(c) *Respiratory passages*.—The secretions of the nose, throat and of the bronchi are diminished: the sputum becomes dry and expectoration is made difficult.

(d) *Stomach, Intestine and Pancreas*.—The secretions are diminished. In the stomach, the secretion of hydrochloric acid is markedly diminished but not as much of mucin and enzymes; pancreatic secretion is also markedly diminished. [Atropine is frequently used in gastric ulcer, a condition associated with an increased secretion of acid in the stomach]. Biliary secretion is only moderately affected.

(e) *Lachrymal Glands*.—The secretion of tears is diminished.

(f) *Other Secretions* as of the **mammary glands, suprarenal** and of the **lymph** are not altered. On the inflamed breast of a nursing mother belladonna preparations are frequently applied¹³⁸. The beneficial effects are more from the support provided than from any direct drug action.

(435) R
Pot. Brom. gr. 10
Pot. Iod. gr. 2
Tinct. Bellad. min. 10
Ext. Grindel. Liq. min. 15
Tinct. Lobel. Ether. min. 15
Aq. Ment. Pip. ad. fl. oz. 1
Ev. 2 to 4 hours for asthma.

(436) R
Pot. Brom. gr. 2½
Tinct. Bellad. min. 2
Tinct. Opii Camph. min. 5
Syr. Tolu. min. 20
Aq. Chlorof. min. 120
For whooping cough in a child.

(437) R
Atrop. Sulph. gr. 1
Morph. Sulph. gr. 8
Acid. Sulph. Aromat. min. 120
Aq. Ment. Pip. ad. fl. oz. 1
(Waston)
Five drops every 3 hours for night sweats.

(438) R *Collodium Belladonnae*
Ext. Bellad. Liq. 50
Canada Balsam 4
Ol. Ricin. 2
Camphora 1·5
Pyroxylin. 2·5
Etheris ad. 100
To apply as required.

(3) **RESPIRATION.**—(a) In therapeutic doses, it has either no obvious action or slows the respiration by depressing the afferent vagal endings in the lungs and also dilating the bronchioles, allowing an easy entry of the air. (b) In bigger doses, it stimulates the medullary centre and respiration becomes quicker and slightly deeper. (c) In toxic doses, death follows from respiratory paralysis.

(4) **TEMPERATURE.**—Given in a moderately big dose, the temperature is slightly raised in spite of increased loss of heat from dilatation of the skin-vessels. Probably this is due to its direct action on the heat centre in the corpus striatum and to suppression of sweating.

(5) **EXCRETION.**—Atropine is rapidly absorbed and enters into most of the organs. Nearly half of the atropine taken internally is excreted in the urine and the rest is oxidised probably in the liver into tropic acid and tropine. A trace may appear in the milk.

(6) **IDIOSYNCRASY and TOLERANCE.**—A few individuals are hypersensitive to atropine and even a therapeutic dose orally or its prolonged administration in eye practice causes dryness of the mouth, palpitation, nervous excitement and dilatation of the pupil. The children stand it fairly well.

Some animals especially a rabbit, can stand a high dose of it. A moderate degree of tolerance is acquired by its prolonged administration.

SUMMARY.—Atropine (i) depresses the *parasympathetic nerve-endings* in the (a) **involuntary muscles** especially when these are in spasmodic condition as in the bronchioles, intestine, bile and the urinary passages: (b) in the **eye**, causing paralysis of the 3rd nerve-endings (dilatation of the pupils and paralysis of accommodation): (c) on the **heart** causing vagal paralysis and quickening the heart rate: (d) in **secretory glands**, especially lessening the secretion of sweat and gastric acidity. (ii) It acts on the *medullary centres* causing respiratory stimulation (slightly vaso-motor and temporary vagal stimulation also) and (iii) on the *peripheral sensory nerve-endings* causing slight analgesia: (iv) It is a *cerebral excitant* with after-depression in toxic doses.

Homatropine Hydrobromide

It has roughly the same action as atropine, but is much less active. It is solely used in eye practice in 1 to 2% solution to cause **dilatation of the pupil** for the examination of the fundus. This dilatation takes place and passes off much more quickly than that of atropine, the pupil becoming nearly normal in about twenty-four hours, whereas atropine takes several days for its action to pass off. But in some cases, it does not completely paralyse the accommodation and is therefore inferior to atropine. As the action is short-staying, the **intra-ocular tension** does not go up.

In eye practice, watery solution of the salt, oily solution of the alkaloid, ointment or eye disc may be used^{439, 440}.

HYOSCYAMUS (*Hyoscy.*), *Hyoscyami folia*, Henbane leaves

Dried leaves and flowering tops of *Hyoscyamus niger*, collected from the flowering plant. The seeds were used in Indian medicine in the name of *Khorasani Yamani*. Obtained from the forests of Jammu and Kashmere and also from Saharanpur. These leaves are pale greyish-green, ovate or elongated triangular, with coarsely dentate margins and bear glandular hairs: laminae about 25 cm. long: if petiolated, about 30 cm. long: have a characteristic strong odour and bitter and slightly acid taste.

These contain not less than 0.05% of the alkaloids calculated as hyoscamine.

The alkaloids are *hyoscyamine*, *hyoscyne* and a trace of *atropine*.

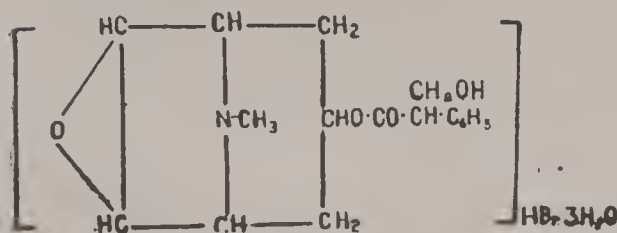
HYOSCYAMI PULVIS (*Hyosc. Pulv.*): green or greyish green powdered *hyoscyamus*.

OFFICIAL PREPARATIONS.—(i) **Extractum Hyoscyami Liquidum** (*Ext. Hyoscy. Liq.*), See p. 40. *Standardised* to contain 0.05% w/v of alkaloids calculated as hyoscyamine. Dose, 3 to 6 minims or 0.2 to 0.4 ml. (ii) **Extractum Hyoscyami Siccum** (*Ext. Hyoscy. Sicc.*), See p. 39. It is *standardised* to contain 0.3% of total alkaloids. Dose, $\frac{1}{4}$ to 1 grain or 16 to 60 mg. (iii) **Pillula Colocyntidis et Hyoscyami** (*Pil. Colocynt. et Hyoscy.*), See p. 52. Dose, 4 to 8 grains or 0.25 to 0.5 gramme. (iv) **Tinctura Hyoscyami** (*Tinct. Hyoscy.*), See p. 59. *Standardised* to contain 0.005% w/v of hyoscyamine. Dose, 30 to 60 minims or 2 to 4 ml. 60 min. contains $\frac{1}{320}$ gr. of total alkaloids.

HYOSCYAMINÆ SULPHAS (Not official).—This is obtained from various plants of the belladonna group, especially from *hyoscyamus*.

Dose, 1/200 to 1/100 grain or 0.0003 to 0.0006 gramme.

HYOSCINÆ HYDROBROMIDUM (*Hyoscin. Hydrobrom.*), Hydrobromide of Hyoscine, Scopolamine hydrobromide, $C_{17}H_{21}O_4N$, HBr, $3H_2O$.



This is the hydrobromide of the alkaloid *l*-hyoscine and is obtained from various plants of the belladonna group. Colourless transparent, rhombic crystals, freely soluble in water and alcohol (90%).

Dose, 1/200 to 1/100 grain or 0.3 to 0.6 mg.

(i) **Injectio Hyoscinæ Hydrobromidi** (*Inj. Hyoscin. Hydrobrom.*), See p. 44.

Dose as of Hyoscine Hydrobromide: if strength is not stated, one containing 1/160 gr. in 15 min. or 0.4 mg. in 1 ml. is dispensed.

(ii) **Oculentum Hyoscinæ** (*Oculent. Hyoscin.*), See p. 51. (0.125%).

INCOMPATIBLES.—Alkalies, vegetable acids, silver nitrate and lead acetate.

(439) B
Homatrop. Hydrobrom. gr. 2
Aq. Dest. fl. oz. $\frac{1}{2}$
Lotion: To drop into the eye.

(440) B
Homatrop.
Cocain. aa. gr. 4
Ol. Ricin. Steril. fl. oz. 1

STRAMONIUM (*Stramon.*), Stramonium leaves

The dried leaves and flowering tops of *Datura Stramonium* and of *Datura Tatula* containing alkaloids, mostly *hyoscyamine*, a little of *atropine* and *hyoscyne*. The total alkaloids are sometimes called *daturine* which should not be less than 0.25% calculated as *hyoscyamine*.

Leaves are greyish green, thin, twisted and brittle when dry, 3 to 10 inches long and $2\frac{1}{2}$ to 5 inches wide (8 to 25 cm. \times 7 to 15 cm.), acuminate apex, dentate margins and unequal at the base: ovate and shortly petiolate; flowers solitary: odour unpleasant and taste bitter.

STRAMONII PULVIS (*Stramon. Pulv.*), greyish green powder of stramonium.

OFFICIAL PREPARATIONS.—(i) **Extractum Stramonii Liquidum** (*Ext. Stramon. Liq.*), See p. 40. *Standardised* to contain 0.25% w/v of the alkaloids of stramonium, calculated as *hyoscyamine* (3 min. contain about 1/120 gr.). DOSE, $\frac{1}{2}$ to 3 minims or 0.03 to 0.2 ml. (ii) **Extractum Stramonii Siccum** (*Ext. Stramon. Sicc.*), See p. 39. *Standardised* to contain 1% of the alkaloids. DOSE, $\frac{1}{4}$ to 1 grain or 15 to 60 mg. In post-encephalitic and similar conditions, 1 to 8 grains or 60 to 500 mg. (iii) **Tinctura Stramonii** (*Tinct. Stramon.*), See p. 60. *Standardised* to contain 0.025% w/v of the alkaloids, calculated as *hyoscyamine*. DOSE, 5 to 30 minims or 0.3 to 2 ml.: in 30 min. about 1/120 gr. of the alkaloids.

Pharmacology [and Therapeutics]

STRAMONIUM has the usual *anticholinergic* belladonna action but is more commonly used as **anti-spasmodic** in bronchial asthma, by inhalation (powdered leaves)^{441, 442} as well as orally (extract or tincture^{443, 444}).

Recently, the tincture is being used to lessen salivation, tremor and muscular spasm of encephalitis lethargica and Parkinsonism (p. 606). Starting with 10 minims three times daily, the dose is increased to 60 minims (Hurst and Hall). If an excessive dryness of the mouth and blurred vision are complained of, 1/10 grain of pilocarpine nitrate is given with the last dose. The dose of the latter is also gradually increased, perhaps up to 2/5 grain. The solid extract is prescribed in pill form.

Hyoscyamine

Atropine and *hyoscyamine* act in the same way and with nearly equal potency on the *central nervous system* in the

- | | |
|---|---|
| <p>(441) R Pot. Nit. Stramonium. Lobelia. Anis. aa. oz. 1 (Lond) Fumes of 60 grs. of the burnt powder are inhaled for bronchial asthma.</p> | <p>(443) R Pot. Iod. gr. 3 Tinct. Stramon. min. 10 Tinct. Lobel. Æther. min. 15 Ext. Glycyrrh. Liq. min. 20 Sp. Chlorof. min. 15 Aq. ad. fl. oz. 1 For bronchial asthma.</p> |
| <p>(442) R Pot. Nit. Lobelia. Stramon. Camell. Sinens. aa. oz. 1 Ol. Eucalyp. min. 10 Pulv. Fumes of burnt powder are for inhalation.</p> | <p>(444) R Ephedin. Hydrochlor. Ext. Stramon. Sicc. Phenobarbiton. aa. gr. $\frac{1}{2}$ Aminophyllin. gr. $1\frac{1}{2}$ Glycer. Trag. q.s. Pil. For asthma.</p> |

mammals. But hyoscyamine is twice as powerful as atropine in its action on the *peripheral nerve-endings* in the salivary glands, heart and the pupil. It is hardly obtained in pure form for therapeutic administration, being readily changed into atropine.

Atropine contains an equal part of each of *l*-hyoscyamine and *d*-hyoscyamine: both are active on the central nervous system and *l*-hyoscyamine only on the peripheral nerve endings: this accounts for the difference of action between atropine and hyoscyamine.

Tincture and extracts of hyoscyamus are frequently used for *peripheral action* as antispasmodic to unstriated muscle fibres like belladonna. On account of the presence of hyoscine it has a little of *central sedative action* also and two together make it a more powerful antispasmodic: often used with strong purgatives to control gripes.

Hyoscine or Scopolamine

Hyoscine also closely resembles atropine in its *peripheral action*. But it acts **more powerfully and quickly**. It dilates the pupil and paralyses accommodation more rapidly than atropine. It reduces the glandular secretions also. It paralyses the vagal endings in the heart but not with the usual therapeutic dose of 1/100 grain which may not slow the pulse. Its actions are comparatively short-staying (less sustained anticholinergic action) and probably it is oxidised or excreted more quickly.

Its action on the *central nervous system* is very different. Even in a minute dose, sometimes with a stage of slight excitement and often without any, it causes **motor relaxation** and a feeling of **drowsiness** followed by sleep usually lasting for 5 to 8 hours. The usual dose, as 1/150 grain is not followed by any after-effect. But a big dose without any greater soporific effect may cause dryness of the throat, mental confusion and delirium like atropine. It has **no stimulating** effect on the **medulla**: the respiratory centre is depressed the breathing being made slow and weak.

Thus in *peripheral action*, atropine and scopolamine have *quantitative difference*. Atropine acts more powerfully and for a longer period on the heart, intestine and bronchial musculature and scopolamine is stronger on the iris, ciliary body and secretory glands (salivary, bronchial and sweat).

On account of strong *central sedative action*, except locally for the *eye*, scopolamine is not used for peripheral action and atropine is more commonly used.

[Hyoscine hydrobromide is often used as a cerebral depressant in cases of delirium, mania and sleeplessness due to motor excitement⁴⁴⁵. An injection of hyoscine with morphine is occasionally given instead of chloroform for minor surgical

operations. In order to minimise the pains of childbirth, $\frac{1}{6}$ grain (10 mg.) of Morphine with $\frac{1}{200}$ grain (0.3 mg.) of Hyoscine is given hypodermically. One hour after, $\frac{1}{450}$ grain of the latter is given and this may be repeated every four hours if required. The labour goes on but the pain is only slightly felt, the patient being in a drowsy condition, called "twilight sleep". Both morphine and hyoscine are respiratory depressants which may have action the foetus. Pethidine-scopolamine or pethidine-hyoscine (see p. 523 and 551) is getting more popular.

In order to minimise the excitement stage of anaesthetics like chloroform or ether, $\frac{1}{200}$ grain of scopolamine with $\frac{1}{6}$ grains of morphine is sometimes given beforehand as a basal narcotic. The patient goes under the anaesthetic without a period of struggle.

It is also given in parkinsonism in increasing doses from $\frac{1}{150}$ gr. to $\frac{1}{50}$ gr. hypodermically or orally, may be combined with caffeine to prevent sleepiness. (See p. 606). Bigger doses cause respiratory depression.

To minimize sea-sickness and air-sickness, 0.1 mg. tablets of scopolamine camphorate or 0.4 mg. of hyoscyamine camphorate may be used.

For eye conditions to dilate the pupil, 1% watery solution or official eye ointment may be used : acts more quickly and for a shorter time than atropine.

BELLADONNA POISONING.—This may be due to swallowing belladonna liniment by mistake : taking atropine orally in ascending doses, conjunctival application in over strength (drug entering the nose by naso-lachrymal duct and absorbed).

Idiosyncrasy is more obvious with scopolamine than with atropine.

Symptoms.—(a) Dose of atropine, 0.5 mg. : slight cardiac slowing and dryness of the mouth. (b) Dose 1 mg. : marked dryness of the mouth and thirst : slowing of the heart followed by palpitation : slight dilatation of the pupil. (c) Dose 2 mg. : xerostomia, quick heart rate, skin dry, pupils dilated and near vision blurred. (d) Dose 5 mg. : the above symptoms are more marked with dysphagia and dry skin : headache, restlessness and disturbed speech. (e) Dose 10 mg. : Eye changes, diminution of glandular secretions, quickening of cardiac rate and nervous symptoms are more marked (restlessness, excitement, hallucination, delirium, ataxia and coma). (f) Fatal dose is near about 160 mg.

Treatment.—Stomach wash : pilocarpine : sedatives as barbiturates and chloral hydrate : for respiratory failure, O₂ with CO₂ inhalation and analectics. (See p. 556).

SUMMARY.—Belladonna Group of drugs are used as follows : (i) as local analgesic, belladonna extract : (ii) for pupil dilatation and paralysis of accommodation, atropine and hyoscine : (iii) as involuntary muscle relaxant, atropine, stramonium (for broncho-spasm) and tincture of hyoscyamus (intestinal spasm) : (iv) to lessen glandular secretion, atropine, (gastric acidity, salivation and perspiration) : (v) as respiratory

(445) B

Hyoscin. Hydrobrom. gr. $\frac{1}{150}$

Morph. Sulph. gr. $\frac{1}{4}$

Aq. pro Inj. min. 15

For hypodermic injection.

stimulant, atropine : (vi) for cerebral sedation, hyoscine : (vii) for parkinsonism, stramonium and hyoscine and (viii) for bradycardia and heart-block and in vagotonia, atropine.

Non-official and Proprietary Preparations

BELLAFOLINE, *l*-hyoscyamine or atropine is available as 0.25 mg. tablets, solution (10 min. has 0.25 mg.) and ampoule, 1 c.c. has 0.5 mg.

BELLADENAL tablet contains 0.25 mg. (1/250 gr.) of belladonna alkaloids (*l*-hyoscyamine) and phenobarbitone, 50 mg (3/4 gr.) : peripheral parasympathetic inhibitor and central sedative : vasodilating and spasmolytic. Used in gastro-duodenal ulcer, spastic colitis and spastic constipation : urogenital spasm : sea and air sickness : uncontrollable hiccough : vascular spasm also epilepsy, chorea and anxiety neurosis : 2 to 3 tablets daily,

BELLERGA tablet contains ergotamine tartrate 0.3 mg., belladonna alkaloids 0.1 mg. and phenobarbitone 20 mg. Sympathetic, parasympathetic and brain stem sedative. Used in neuro-vegetative distonia, neuroses, menstrual disorders, thyrotoxic state and in nervous dermatoses. Begin with 4 tablets a day and lessen.

EUMYDRIN, methylatropine, atropine methonitrate, is sometimes used in eye practice : more often it has been used in congenital pyloric stenosis : 1 mg. dissolved in 10 c.c. is used, 2 c.c. to start 1/2 hour before each of the 7 feeds. It is said to be 50 times less toxic than atropine. It is also used in pyloric and cardiospasm in an adult in 0.5 mg. dose 3 to 4 times daily.

NOVATROPINE, homatropine methyl bromide, in 2.5 mg. (1/24 gr.) tablet is given 3 or 4 times daily before food for gastro-intestinal colic and hyperchlorhydria. It has less central action.

BULBOCAPNINE (Dose, 1 1/2 grains) and **BANISTERINE** (Dose, 1/2 grain) allied to hyoscine are useful in parkinsonism.

SYNTROPHAN (Roche) is a synthetic antispasmodic (Dose, 0.05 g. tablet t.i.d. or hypodermically 0.01 g. in one ml.) useful in hypertension, angina pectoris, coronary spasm, gastro-intestinal spasm and dysmenorrhœa.

TRASENTIN (Ciba) another synthetic compound is useful in gastric, pyloric and duodenal spasm, intestinal, renal and biliary colic and in dysmenorrhœa, available in tablets (0.075 g.), suppository (0.1 g.) and ampoules (0.075 g. in 1 1/2 ml.).

Neuro-Transentin, each tablet has 0.02 g. each of trasentin and phenobarbitone : antispasmodic, sedative and hypnotic. *Spasmocibalgine*, 0.05 g. trasentin and 0.25 g. cibalgine in 0.3 g tablets : analgesic and antispasmodic.

DEPROPANEX (a deproteinized pancreatic extract) in 10 c.c. vial for relieving acute contraction of the smooth muscles : in renal colic 3 to 5 c.c. : in primary dysmenorrhœa, 2 to 4 c.c. : in thrombo-angiitis obliterans 2 to 3 c.c. daily or every other day.

AGARICIN, prepared from a fungus growing on larch tree, in 1/2 to 2 grains dose diminishes the secretion of sweat and is given for night sweat ; it may also be combined with atropine⁴⁶.

GRINDELIA.—The liquid extract is prescribed in 10 to 20 minims doses. This contains an amorphous resin whose action resembles the same of belladonna group, *relaxing the muscular coats* of the bronchial mucous membrane ; further it acts as an *expectorant*⁴⁷. It is not definitely known how it acts.

(446) B

Agaricin. gr. 1
Atrop. Sulph. gr. 1/100
Lactosum gr. 5
Pulv. For night sweats.

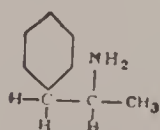
(447) B

Ephed. Hydrochlor. gr. 1/2
Ext. Grindel. Liq. min. 15
Ext. Kuth. Liq. min. 30
Syr. Tolu. min. 60
Aq. Chlorof. ad. fl. oz. 1
For bronchial asthma.

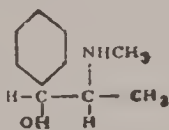
It is, often, a popular remedy for *bronchial asthma* both during the paroxysm itself and also in the period of interval to prevent its further recurrence. For a similar reason, it is also useful in chronic bronchitis which is often associated with a certain amount of spasmodic condition of the bronchial tubes.

C. DRUGS STIMULATING THE SYMPATHETIC NERVE-ENDINGS

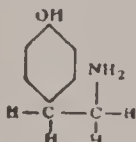
The drugs stimulating the sympathetic nerve endings include *adrenaline* and *ephedrine* also several others recently synthetically prepared: of the latter the most important is *amphetamine*.



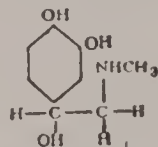
Amphetamine



Ephedrine



Tyramine



Adrenaline

Although these are called sympathomimetic drugs, only adrenaline is really so and others are only partially.

ADRENALINA (*Adrenal*), Adrenaline, Epinephrine, 1- α -3 : 4-dihydroxyphenyl- β -methylaminoethanol, $C_9H_{13}O_3N$

This is the active principle of the medulla of the suprarenal glands of certain mammals, prepared from an acid extract or by synthesis. This is a colourless or pale buff-coloured sphæro-crystalline powder, sparingly soluble in water but freely so in solution of sodium and potassium hydroxide and watery solution of mineral acids and boric acid. It is unstable being easily destroyed in neutral or alkaline solution. It is lævorotatory to polarised light. First isolated in crystalline form by Takamine (1901).

Dose, 1/600 to 1/120 grain or 0.1 to 0.5 mg. by subcutaneous injection.

OFFICIAL PREPARATIONS.—(i) *Injectio Adrenalinæ* (*Inj. Adrenal.*), See p. 42. This is used in the preparation of *Inj. Procaïn. et Adrenal. Mit.* Dose, 2 to 8 minims or 0.12 to 0.5 ml. (ii) *Liquor Adrenalinæ Hydrochloridi* (*Liq. Adrenal. Hydrochlor.*), See p. 49. It should be stocked in a specially prepared glass bottle, well filled and well-corked and protected from light. This is used in the preparation of *Inj. Procaïn. et Adrenal. Fort.*

Pharmacology [and Therapeutics]

The active principle of the adrenal medulla, ADRENALINE, which is also now prepared synthetically, produces effects resembling what follow the stimulation of the entire sympathetic nervous system excepting those supplying the cutaneous glands and in many respects, are opposite to the effects of the stimulation of the vagus. This stimulating action is produced not exactly on the anatomical ends of the sympathetics but on some substance between the nerve-ending itself and the contractile substance of the muscle, called the **myo-neural junction**. Adrenaline does not act directly on the muscles either, for when the sympathetic nerve-endings are paralysed

by apocodeinè, adrenaline fails to act although the muscles concerned are responsive to direct stimulation.

This action in brief is manifested as acceleration of heart beat, rise in blood pressure, dilatation of the pupils, inhibition of the stomach, intestine and the urinary bladder and liberation of glucose from the liver.

The sympathetic system has two sets of fibres acting differently; these are the (i) motor *excitatory* and (ii) *inhibitory*. The action of adrenaline is different in different parts of the body and under different circumstances according to this innervation, whether one kind is predominating or the other.

CIRCULATION.—Given by intravenous injection, several important actions are seen on the circulatory system. There is a rapid marked rise in the blood pressure with quickening of the pulse rate. Soon the rate it is slowed down, followed by quickening again. This acceleration is associated with increased irritability of the heart muscles, predisposing it to ventricular type of extrasystole, even fibrillation. [This risk is great if adrenaline is administered for heart failure in the early stage of chloroform anæsthesia: See p. 465].

This rise of blood pressure is due to constriction of the arterioles by direct local action on the vessel wall through myoneural junction, most marked in the splanchnic area also lessening of the quantity of blood in the spleen, viscera and large veins, thus increasing the blood volume in the peripheral circulation. The arteries of the limbs are less involved and the pulmonary, cerebral and cardiac ones are least affected. In fact, the coronary arteries are momentarily slightly dilated. The adrenaline effect is apparently proportionate to the amount of physiological control exercised by the vaso-constrictor nerves. The veinules are also slightly constricted; in the liver this is more marked in the hepatic than in the portal system. This rise of blood pressure is of short duration and in a few minutes it comes down and may even go below the original level.

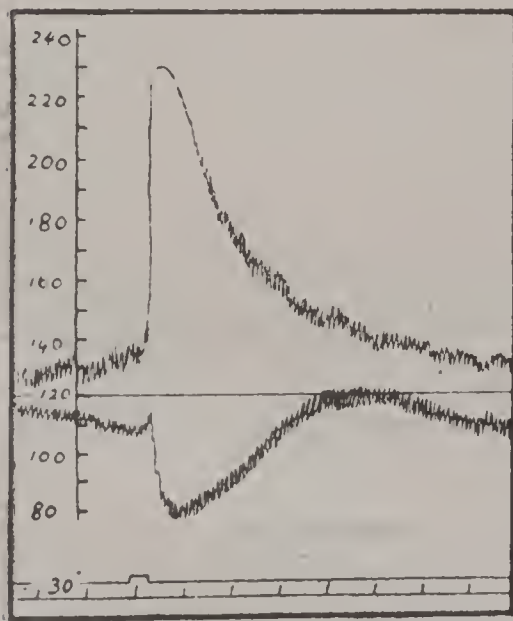


Fig. 46.—The upper curve shows the effect of 0.025 mg. of adrenaline before and the lower curve, of 0.1 mg. of adrenaline after 10 mg. of ergo-toxine (After Dale from Dixon).

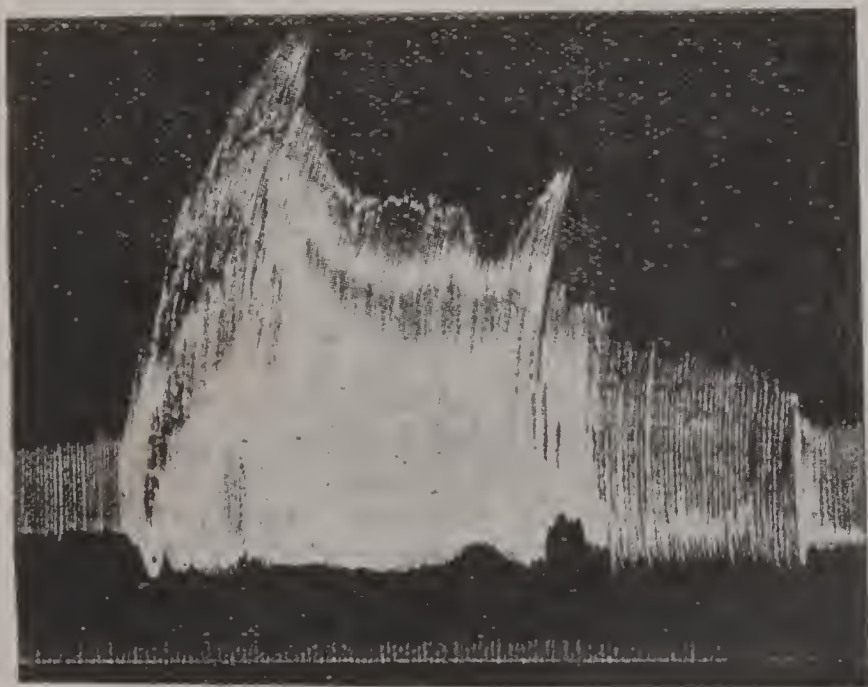
Raised blood pressure stimulates the carotid sinus causing secondary vasodilatation, slowing of the heart rate and fall in the blood pressure.

On account of vaso-constriction some plasma escapes from the blood causing concentration : this raises the red blood cell count.

In some cases, after an injection of adrenaline, instead of a rise in blood pressure, there is vaso-dilatation and distinct fall of it especially of the diastolic pressure. This sometimes happens when either a comparatively smaller dose is given subcutaneously to a case with high blood pressure or when the sympathetic nerve-endings have been previously paralysed by a big dose of ergotoxine. This reversal of adrenaline reaction is explained in two ways :

(i) Adrenaline not only stimulates the vaso-constricting, but also the vaso-dilating nerve endings and more powerfully the former. But when the dose is insufficient to cause vaso-constriction or the vaso-constricting nerves are exhausted or paralysed, the other set (namely, the vaso-dilating ones), is activated. This causes a fall in the blood pressure.

(ii) Adrenaline constricts the arterioles and increases the cardiac output but dilates the capillaries ; so when the former actions fail, the latter becomes more apparent (Dale) causing a fall in blood pressure. This theory is getting more corroboration.



(Dixon)

Fig. 47.—The effects of adrenaline solution on the heart ; marked quickening and increased force of the heart beat.

The quickening of the heart rate following a subcutaneous injection of 0.5 to 1 mg. of adrenaline is due to stimulation of the sympathetic nerve-endings in the heart muscles resulting in quicker and more forcible beats. The cardiac output also

increases. But if this is very much quickened, as after a big dose of adrenaline, on account of incomplete filling during diastole, the cardiac output is diminished and the blood pressure falls. [Adrenaline has been found useful in *heart-block* : this is believed to stimulate the ventricular pace makers and sensitize the auriculo-ventricular bundle. The recommended dose is 0.5 mg. subcutaneously, repeated as required : in more severe cases, 0.05 mg. intravenously and in desperate cases of cardiac standstill, 0.25 mg. intracardially]. (Roelsen, 1949).

Thus the blood pressure depends on the dose of adrenaline chloride and its action on the cardiac output, contraction of the blood-vessels and dilatation of the capillaries.

LOCAL ACTION.—This **vaso-constricting action** is also very marked if adrenaline is directly applied on a superficial blood vessel. Dropped into the conjunctiva, this looks blanched. Injected subcutaneously, it causes local devascularisation and so the drug is slowly absorbed. The effects on the cardiovascular system therefrom, are not manifested unless a bigger dose, as at least 15 minims, is given.

[Injected subcutaneously with a local anæsthetic, minor operations may be performed bloodlessly and painlessly. It is also frequently applied to bleeding surfaces, especially if there is only slight oozing from the smaller arterioles. Even 1 in 50,000 solution is fairly effective. Adrenaline spray is useful in various conditions of naso-pharyngeal turgescence and bleeding].

RESPIRATION.—Raised blood pressure caused by adrenaline given intravenously may result in **irregular respiration**, quick and forcible breathing alternating with periods of apnœa “adrenaline apnœa” (carotid sinus effect).

BRONCHIAL MUSCLES.—These **relax** and the bronchioles widen, due to stimulation of the sympathetic nerve-endings which are the inhibitors of the contracting muscles of the bronchi. The breathing capacity is increased also the respiratory volume and the residual air diminished. Adrenaline is of great value in bronchial asthma and in other spasmodic conditions of the bronchioles and 0.5 c.c. or less subcutaneously may give temporary relief.

KIDNEYS.—From general vaso-constriction involving all viscera restricting the blood-supply, the secretion of urine is at first markedly reduced ; but as the renal vessels relax quicker than those of the other organs, the circulation through the kidneys soon increases, increasing at the same time the quantity of urine. Therefore it is a **diuretic** of entirely vascular origin being dependent on the increased circulation through renal and other blood vessels.

The secretion of other glandular structures is either not affected or markedly reduced owing to vaso-constriction and

diminished blood-supply. A viscid saliva is secreted (stimulation of the sympathetic : See fig. 37).

STOMACH AND INTESTINE.—The normal function of the sympathetics is to **inhibit** their muscular contraction, but increase the motor activity of the different sphincters as the pyloric, ileocaecal and the sigmoidal sphincters and also of the muscularis mucosæ.

An intravenous injection of adrenaline consequently stops the peristaltic movements of the stomach and the intestine which are relaxed completely and their various sphincters as pylorus, ileo-colic and internal anal sphincters are kept contracted, these being innervated by sympathetic motor nerves.

In the same way, the **gall-bladder** is relaxed but the bile duct is contracted : the **urinary bladder** is also relaxed, although its sphincter, the ureters, vas deferens and the seminal vesicles are somewhat contracted.

UTERUS.—This contains two sets of autonomic fibres, the *motor excitatory* causing contraction and the *inhibitory* causing relaxation of the uterus. The adrenaline action depends on the type of the animal and phase of the uterus. In some animals the uterus is always contracted and in others nongravid uterus is relaxed and the gravid one contracted. Human uterus is usually contracted at all stages but this action is not marked. Given in a big dose, uterine contraction is first markedly increased and then diminished.

Thus nervous predominance differs in different animals both in the pregnant and non-pregnant states and the effects of the adrenaline also consequently vary.

EYE.—Given by intravenous injection, adrenaline constricts the superficial blood vessels of the conjunctiva, **dilates the pupil**, widens the palpebral fissure and protrudes the eyeball, producing effects similar to those following the stimulation of the cervical sympathetics.

Applied locally, superficial blood vessels are constricted, pupil is dilated and intraocular tension is momentarily lessened.

SPLEEN.—The muscles of the spleen are **contracted** by it, reducing the volume. [This action is sometimes taken advantage of for driving malarial parasites from spleen into the general circulation and is a helpful preliminary procedure in blood examination, when the parasites are not found in the usual way].

BONE MARROW.—Adrenaline causes contraction of the vascular spaces resulting in temporary increase of red blood corpuscles and hæmoglobin.

METABOLISM.—Adrenaline favours **glycogenolysis** in the liver by stimulating the sympathetic nerve-endings, raising the blood sugar level [and is therefore useful in hypoglycæmia following an overdose of insulin].

With this, the **basal metabolism is increased** followed by increased heat production. The skeletal muscles quickly recover from fatigue.

But the action of adrenaline is short-staying as it is quickly fixed by tissues, destroyed by amine oxidase and disappears.

PRACTICAL THERAPEUTIC USES

The practical uses are mainly for local *vaso-constriction*, relaxing the *bronchioles*, stimulating the *heart* and causing *glycogenolysis*.

(i) It is applied locally or injected subcutaneously to **stop capillary bleeding**, for making minor and superficial *surgical operations* nearly bloodless and for intensifying the action of local anæsthetics by delaying their absorption. It is frequently used for *bleeding from the nose* and also sometimes for the same from a *gastric ulcer* (by oral administration in bigger doses). A suppository may be useful in *bleeding piles*. For an internal bleeding, it is unsuitable owing to the rise of systemic blood pressure that follows.

(ii) It is injected subcutaneously for a prompt relief of bronchial **asthma** by causing relaxation of the bronchioles. A dose of $\frac{1}{2}$ c.c. or less may be sufficient but as the action is short-staying, it has to be frequently repeated. One in 100 solution specially in oil is sometimes sprayed into the nose and throat with a nebuliser: 2 mg. in 1 c.c. dose is given intramuscularly also and has prolonged effect. Nasal spray is also useful in hay fever and in coryza.

NEBULA ADRENALINÆ ET ATROPINÆ COMPOSITA B.P.C., has adrenaline 4.57 g., atropine methonitrate 1.14 g., papaverine hydrochloride 8 g., chlorbutol 4.5 g., tartaric acid 3.65 g., sodium metabisulphite 1.14 g. and distilled water to 1000 ml.

It is also similarly given in various **anaphylactoid conditions** as angioneurotic oedema, urticaria and serum sickness and also in **nitritoid crisis** following arsenobenzol injections.

An intravenous injection often causes a marked quickening of the pulse rate and distressing palpitation. So it should be given very slowly and preferably well diluted with normal saline.

(iii) It is also given in **sudden heart failure** as from sudden syncope and is even injected directly into the heart muscles for the immediate increase of the force and frequency of the heart beat.

Care should be taken not to give it during the early stage of chloroform anæsthesia or in cyclopropaine anæsthesia for fear of inducing ventricular fibrillation.

In conditions associated with low blood pressure, it is freely given, as in cholera and acute bacillary dysentery. It is also useful in malaria and kala-azar with low blood pressure and is given before the intravenous injections of quinine and antimony compounds.

(iv) It is helpful in **hypoglycæmic shock** from an overdose of insulin (see p. 415). Glycogen from the liver is released to raise the blood sugar to its normal level.

(v) Except for local action on the stomach, it is useless to give it by the mouth. It may be given per rectum, but should not be mixed with an alkali. A rectal saline drip with 30 to 60 minims of adrenaline chloride solution may be given for slow and sustained absorption. No dependable amount may be absorbed from the sublingual space.

Adrenaline hydrochloride solution, if exposed to light and air, turns red and becomes inert and so such red samples should be discarded.

Non-official Preparations

ALUDRINE, ALEUDRIN, ISONORIN, ISORENIN, ISOPRAL and NORISODRINE are in various names isopropyl modification of adrenaline and are more powerful broncho-dilator without causing a rise in blood pressure (rather moderate fall) : used in $\frac{1}{2}\%$ spray or in 10 mg. linguete for bronchial asthma.

SYNEPHRIN AND NEOSYNEPHRIN are synthetic products resembling adrenaline. The former is a better vaso-constrictor.

The latter causes more prolonged rise of blood pressure and is also a powerful vaso-constrictor having direct action on the muscles of the blood vessels. This is a stable preparation and is capable of both oral and parenteral administration. This has been used in supraventricular tachycardia is a dose not exceeding 0.5 mg. intravenously.

PROPADRINE, a sympathomimetic amine is used as 25 or 50 mg, capsule, 0.66% nasal jelly and 1 to 3% aqueous solution for adrenaline action.

PRIVINE an imidazoline derivative, a non-irritant and nontoxic nasal decongestant and antialergent, available as 0.1% solution for nasal and eye drops. This is also available with *cibalzin* 5%.

EVATMINE, a combination of adrenaline and pituitary extract, is given in 1 c.c. doses hypodermically in bronchial asthma.

EPHEDRINA (*Ephed.*), Ephedrine, $(C_{10}H_{15}ON)_2H_2O$

Ephedrine is the hemihydrate of *l*- α -hydroxy- β -methyl-aminopropylbenzene, an alkaloid obtained from *Ephedra Sinica*, *Ephedra Equisetina* and other species of ephedra or prepared by synthesis : contains between 94 to 95% of $C_{10}H_{15}ON$.

Colourless, non-deliquescent, non-efflorescent hexagonal, prismatic crystals, inodorous or with a slightly unpleasant smell.

Readily soluble in water, alcohol (95%), solvent ether and in chloroform ; soluble in 20 of glycerin, 25 of olive oil and 100 of liquid paraffin : only anhydrous alkaloid forms a clear solution.

EPHEDRINÆ HYDROCHLORIDUM (*Ephed. Hydrochlor.*), Ephedrine Hydrochloride, $C_{10}H_{15}ON, HCl$.

This is the hydrochloride of an alkaloid, ephedrine, obtained from *Ephedra Sinica*, *Ephedra Equisetina* and other species of *Ephedra* or by synthesis. Colourless, inodorous, bitter crystals, soluble in water and alcohol (90%).

Dose, $\frac{1}{4}$ to 1 grains or 16 to 60 mg.

Tabellæ Ephedrinæ Hydrochloridi (*Tab. Ephed. Hydrochlor.*), See p. 57. Strength is between 89.5 to 110% of ephedrine hydrochloride.

Dose, is the same as of the above. Each tablet if not otherwise stated should contain $\frac{1}{2}$ grain.

Pharmacology [and Therapeutics]

This alkaloid was originally isolated from a Chinese plant, *Ma Hung* by Nagai in 1887. Its chemical formula and pharmacological action have much resemblance to adrenaline.

The action is either stimulation of the sympathetic nerve endings or *retardation of destruction* of the locally formed adrenergic hormone by combining with amine oxidase.

APPLIED EXTERNALLY, on a *mucous membrane*, ephedrine is a **local vasoconstrictor**. The area looks blanched and the secretions are reduced : if any catarrh or painful swelling is present this is relieved. Applied to a small *bleeding wound surface*, it may stop hæmorrhage. [A saline solution 1 to 5%, occasionally an oily drop is often helpful in rhinitis and sinusitis]. But being more readily absorbed than adrenaline, its action is less marked but more sustained].

GIVEN INTERNALLY, by causing **systemic vaso-constriction**, it raises the blood pressure. It increases the force and frequency of **heart beat** and relaxes the **bronchioles** if these are in spasm. It acts on the *sympathetic myoneural junction* and the *involuntary muscles* are not *directly* acted on.

So the action is, like adrenaline, sympathomimetic and in addition directly on the **skeletal muscles**. Further, small doses of ephedrine potentiates the action of adrenaline but bigger doses antagonize : probably ephedrine combines with and blocks the motor receptors.

On the analogy of inhibitory action of physostigmine on choline esterase, ephedrine is believed to counteract *amine oxidase* which destroys adrenaline like adrenergic substance and the action of ephedrine is really due to adrenaline.

The points of *difference* of ephedrine are, (i) it is more stable and capable of oral administration also ; its effects appear slowly but are more sustained : vaso-constricting action is less marked, vaso-dilatation phase is absent and there is no vaso-motor reversal effect ; (iii) the effect of rapidly repeated dose is progressive diminution of response (*tachyphylaxis*) (iv) it is a cerebral excitant and may cause anxiety neurosis, headache and insomnia : (v) it has a tonic action on the skeletal muscles and (vi) it has less obvious action on the intestinal muscles and glandular secretions. A dose repeated frequently may fail to produce the characteristic action.

HEART.—The action of ephedrine on the heart has been more accurately studied in a *dog* (Meek and Seevers). Given in a small dose, the **heart** is at once **slowed** sometimes with extra systole. This is mainly a reflex effect from the raised blood pressure. If atropine is previously given (to paralyse the *vagus*), the slowing is not marked. This is followed by **tachycardia** by acting on the accelerator nerve endings. In the *human being*, the similar effects are produced and sometimes

throbbing in the head, palpitation and tachycardia especially in susceptible persons. Simultaneous administration of sodium barbitone greatly lessens these effects probably by depressing the central nervous system.

BLOOD-VESSELS.—The **vaso-constriction** is marked especially of the splanchnic blood vessels. From this and from increased cardiac output the **blood pressure rises**. These are less marked but more prolonged (6 or 8 hours) than those of adrenaline. With a bigger dose, the heart rate is much quickened, output diminished and the blood pressure may fall.

Like adrenaline it *dilates the coronary blood vessels* and in an intact dog, marked and sustained increase in coronary blood flow was found (Stoland and Ginsberg, 1934).

[Ephedrine is often prescribed in many conditions of *low blood pressure* and complete *heart block* with tendency to syncope but the initial dose should be $\frac{1}{4}$ or $\frac{1}{3}$ gr. which may be repeated every 4 or 6 hours: it is also prescribed in *anaphylactic shock* and in fall in blood pressure in spinal anæsthesia]. An *over dose* more often causes marked palpitation, precordial pain, flushing of the skin, profuse sweating, muscular weakness, faintness, dyspnœa, insomnia and dilatation of the pupils; sometimes depression of the heart muscle also. It *should not be given* in gross organic heart disease or to a patient under digitalis: it is also contraindicated in coronary thrombosis and hypertension.

RESPIRATION.—The actions are two; dilatation of the bronchioles through peripheral action and stimulation of respiratory centre directly. [Broncho-dilator action is moderate and ephedrine orally (see p. 530) is useful after the severe attack of asthma is somewhat relieved with adrenaline injection and the effect is only required to be kept up. It is also useful to counteract the central depression caused by morphine or phenobarbitone].

NERVOUS SYSTEM.—In addition to respiratory, ephedrine stimulates the **vasomotor, cortical and subcortical centres**. *Toxic effects* are insomnia, nervousness, tremor and restlessness. [It is used to cut short avertin anæsthesia also in narcolepsy and is an analeptic].

INVOLUNTARY MUSCLES.—The muscles of the intestine and urinary bladder are somewhat inhibited and of the sphincters and uterus contracted. Ephedrine is useful in nocturnal enuresis of children. But in an elderly person, full dose may cause urinary retention.

The *pupil* is dilated. A 2 to 5% solution causes the maximum effect in 15 to 30 minutes but light and accommodation reflexes still persist unchanged. The action lasts for 4 to 12 hours.

It has no action on the secretion of sweat and on the body temperature. It is non-cumulative and **not habit-forming**.

[Ephedrine is prescribed as nasal spray or drop^{448,449}, orally and also intramuscularly in bronchial asthma, whooping cough and hay fever⁴⁵⁰. It is also given in many anaphylactoid conditions, shock, sudden heart failure, heart block and in conditions of vascular engorgement as epidemic dropsy⁴⁵¹ and in nerve pain of leprosy]. Sometimes adrenaline and ephedrine are combined in subcutaneous injection: the effects are rapid and more sustained also. It is sometimes prescribed for narcolepsy, a condition associated with much sleepiness. It is also useful in myasthenia gravis along with prostigmin].

SUMMARY.—Ephedrine is a **vaso-constrictor** (locally decongestant on the mucous membranes) and **cardio-respiratory accelerator**: relaxes involuntary muscles (bronchioles, pupil, intestine and urinary bladder): a **cerebral excitant** and **skeletal muscles stimulator**. Note the toxic effects.

INDIAN PHARMACOPŒIAL LIST PREPARATIONS

EPHEDRA is the dried stem of *Ephedra Gerardiana* and *Ephedra Nebrodensis* which grow abundantly in the Himalayas from Western Tibet to Sikkim and contain 1% of the alkaloid. Ephedra has a large proportion of pseudoephedrine which acts directly on the heart muscles, increasing the force and strength of cardiac contractions. *The Liquid Extract* contains 2% w/v of alkaloids (Dose, 20 to 30 min. or 1.5 to 2 ml.) and the *Tincture* contains 0.5% alkaloids (Dose, 90 to 120 min.) and sometimes prescribed in asthma, epidemic dropsy and in many conditions with feeble cardiac action and vasodilation. The tablets of the alkaloid are also available, each containing $\frac{1}{2}$ gr. and are more convenient and dependable.

Non-official Preparations

PSEUDO-EPHEDRINE.—Some varieties of *Ephedra* contain this alkaloid also. It has a distinct stimulating action on the myocardium. Compared with ephedrine, although it has less effect on the blood pressure, it is less toxic and more useful in asthma.

ADRENO-EPHEDRINE.—Adrenaline 1 in 1000 with 2% of ephedrine for local application into mucous membranes also hypodermically administered: useful in asthma, epidemic dropsy and in cardiac asthenia.

EPHAZONE tablets contain ephedrine hydrochloride, theobromine, phenazone, fluorescein and excipient: useful in bronchial asthma.

ORTHOXINE is beta-orthomethoxyphenyl-isopropyl methylamine hydrochloride, 100 to 200 mg. orally every 4 hours in bronchial asthma is nearly as effective as ephedrine but without cardio-vascular or central nervous system disturbance.

SULMEFRINE (*dl*-desoxyephedrine hydrochloride 0.125% with sodiumsulphathiazol 2.05% in sterile aqueous solution is used as *drop* or *spray* in rhinitis

DRINALFA, *d*-desoxyephedrine hydrochloride in 5 mg. tablets usually one daily is indicated in state of mental depression and apathy also

- (448) R
Ephed. Hydrochlor. gr. 4
Sod. Chlor. gr. $4\frac{1}{2}$
Chlorbutol. gr. 2
Aq. Dest. ad. fl. oz. 1
For oronasal spray.

- (449) R
Ephed.
Chlorbutol aa. gr. 4
Ol. Arach. min. 250
Liq. Paraff. Lev. ad. fl. oz. 1
Nasal Drops.

- (450) R
Ephedrin. Hydrochlor. gr. 1
Tinct. Camp. Opiat.
Oxymel Scill. aa. min. 30
Syr. Tolu. ad. fl. oz. 1
Linctus: One tea-spoonful.

- (451) R
Ephed. Hydrochlor. gr. $\frac{1}{2}$
Leptazol gr. 1
Pulv. For myocardial weakness
and low blood pressure.

neurocirculatory asthenia, postoperative depression, collapse, shock, sea sickness, hypotension and migraine : better given in the middle of the day to prevent insomnia.

ZEPHROL, ephedrine cough syrup, one tea-spoonful repeated, used in spasmodic cough. ENDRINE, ephedrine nasal drop and spray.

AMPHETAMINA (*Amphetamin.*), Benzedrine,
 $C_6H_5CH_2CHNH_2.CH_3$.

Amphetamine is beta-aminopropylbenzene, prepared by reduction of the oxime of phenylacetone. This should contain not less than 97% of $C_9H_{13}N$.

A colourless mobile liquid with a slight but characteristic colour and acrid taste. It is slightly soluble in water and more so in solvent ether, alcohols, chloroform and acids. It slowly volatilizes in ordinary temperature.

AMPHETAMINÆ SULPHAS (*Amphetamin. Sulph.*).—Benzedrine sulphate, is prepared by neutralising beta-aminopropyl benzene in alcoholic solution with sulphuric acid. It should contain not less than 98% of $(C_9H_{13}N)_2H_2SO_4$. An inodorous white powder with a slightly bitter taste followed by benumbed feeling : soluble at 20°, in 8.8 of water and 515 of alcohol (95%).

Dose, 1/24 to 1/4 grain or 2.5 to 10 mg.

Pharmacology [and Therapeutics]

The type actions are *adrenergic* and but amphetamine is a more powerful *cortical stimulant*.

LOCAL ACTION.—The base and the carbonate are volatile [and used in 1% spray or inhalation of the vapour available as a convenient perforated tube inhaler] : the vapour causes **vaso-constriction** and lessening of secretion in naso-pharyngeal inflammation. It is used in coryza, acute rhinitis, sinusitis and Eustachian tube blocking. If used too freely, a certain amount being absorbed, may cause cortical stimulation.

The sulphate applied in 1% aqueous solution **dilates the pupil** without affecting intra-ocular tension and accomodations.

SYSTEMIC ACTION.—Orally, non-volatile sulphate in 2.5 to 10 mg. doses (available in 5 mg. tablets) causes stimulation of *cerebral cortex* and *medulla* (vaso-motor and respiratory centres). It is (a) powerful **cerebral excitant** causing increased psychic activity and euphoria, lessening of the sense of fatigue and insomnia. (b) **Blood pressure** is raised and the heart rate somewhat lessened, (carotid sinus effect), sometimes with extra-systoles also. (c) It is a **respiratory stimulant**.

[It is used in *narcolepsy*, profound *narcosis*, depressing *psychopathy* and in *post-encephalitic parkinsonism* (along with scopolamine). It may be used as an *awakening agent* after avertin anæsthesia and may be used combined with phenobarbitone in its prolonged administration for the treatment of epilepsy].

It should not be used in a healthy individual for lessening sleep or fatigue only and prolonged use causes *toxic symptoms*. These are insomnia, headache, hyperexcitability and cardiac and gastro-intestinal disturbances.

INVOLUNTARY MUSCLES.—These are mostly relaxed. The *bronchioles* are dilated and this along with stimulation of the respiratory centre, increases the rate and depth of respiration. The *pupil* is moderately dilated. The effects on *gastro-intestinal musculature* are variable: may be relaxed if in spastic state. *Urinary bladder* is relaxed but the sphincter is contracted: it is sometimes used in nocturnal enuresis of children.

METABOLISM is not appreciably altered. Amphetamine is readily absorbed from the alimentary tract and slowly excreted by the kidneys. Habituation may occur in certain persons.

Amphetamine *should not be prescribed* in hypertension, coronary vascular disease, hyperthyroidism and in a condition of nervous excitement.

POISONING.—The excitement of acute poisoning is best relieved by intravenous injection of a rapidly acting barbiturate.

SUMMARY.—*Locally, decongestant: orally, cerebral and medullary stimulant and spasmolytic of involuntary muscles.*

Non-official Preparations

DEXEDRINE, is Dextro-amphetamine Sulphate, said to produce a sustained sense of well-being without distracting elation, irritability and sense of nervous tension: may be prescribed in 5 mg. tablet once or twice daily for systemic depression.

It is also used to suppress appetite in increasing obesity without causing a feeling of depression. In order to avoid insomnia, it should not be given late in the evening.

METHEDRINE, methyl amphetamine hydrochloride 30 mg. in 1.5 c.c. ampoules is given parenterally for pressor effect in *circulatory depression*. Orally, for *narcolepsy*, 2 to 10 tablets (5 mg. each) daily are usually required.

SIDA CORDIFOLIA (Bala).—Its chief active principle appears to be an alkaloid. A minute dose given intravenously causes a sharp and well-marked rise of blood pressure which is maintained for sometime. The force and frequency of the heart beat also increase. The bronchial muscles are relaxed. So it is likely to be useful in asthma.

SYMPATHOLYTIC AGENTS (Not official)

1. **TETRAETHYLAMMONIUM CHLORIDE or BROMIDE T.E.A.C. or T.E.A.B.** blocks transmission of impulses through the autonomic ganglia.

(i) *Sympathetic blockade* gives rise to a fall in blood pressure, tachycardia and peripheral vaso-dilatation with increased blood flow in the extremities and rise in skin temperature.

(ii) *Parasympathetic block* causes inhibition of gastric secretion and motility, paralysis of accommodation and difficulty in micturition and defæcation.

The *clinical effects* as regards the practical use in (a) hypertension and peripheral vascular diseases and (b) in peptic ulcer have been investigated by giving 100 to 500 mg. intravenously. The results are not uniformly favourable (sudden death has been reported) and the effects are short-staying. The injections must be given in recumbent position for the risk of syncope.

The chloride available as *Etamon Chloride* containing in 20 c.c. rubbercapped phial 0.1 g. per c.c., may be used in 2 to

5 c.c. doses intravenously (maximum dose, 7 mg./kg. of body weight) or 10 to 12 c.c. intramuscularly, this is somewhat painful, (maximum dose, 20 mg./kg. of body weight), in thromboangiitis obliterans, arteriosclerosis obliterans, thrombophlebitis, Raynaud's disease and causalgias : injections are given once or twice daily.

TOXIC EFFECTS are marked fall in blood pressure, tachycardia, rise in skin temperature, lessening of glandular secretions and hyperventilation.

2. **PENTAMETHONIUM IODIDE** has similar action but more potent and more lasting. Intravenous injection of 25 to 100 mg. (usually not to exceed 40 mg.) in a hypertensive patient may cause a fall in blood pressure lasting for several hours. (An excessive fall in pressure may be counteracted by an injection of adrenaline.

3. **DIETHYLAMINOETHANOL**, controls ventricular tachycardia and premature heart beats and causes temporary hypotension. Dose is 2 to 5 g. in slow intravenous drip.

4. **DIHYDROERGOCARMINE**, causes sympatholytic action on the terminal augmentor fibres of the sympathetic nerves in 0.2 to 0.3 mg. dose intravenously and afterwards 2 to 8 mg. orally before breakfast : has been favourably reported in hypertension.

All these are opening out newer possibilities for the treatment of hypertensive and peripheral vascular diseases but yet more advance is necessary.

Drugs Acting on the Muscles

1. Drugs **increasing** the activity of the **striped** (voluntary) muscles :

- (i) By acting on the *central nervous system*.—Caffeine and cocaine (psychic centre) and atropine (motor centre) : picrotoxin (cortex, midbrain and medulla).
- (ii) By acting on the *spinal cord*.—Strychnine, thebaine, ammonia and brucine.
- (iii) By acting on the *motor nerve endings*.—These are cholinergic drugs as acetylcholine, carbachol, physostigmine and prostigmin also ephedrine and potassium ion ; calcium ion deficiency.
- (iv) By acting on the *muscles directly*.—Caffeine, veratrine, barium ion and potassium ion.

Adrenaline probably also acts directly to increase the tension in the individual fibres of the skeletal muscles (Brown and others 1948).

2. Drugs **diminishing** the activity of the **striped** (voluntary) muscles :

- (i) By acting on the *central nervous system*.—General anaesthetics, narcotics, hypnotics (especially bromides and barbiturates) and phenytoin also phenazone.

- (ii) By acting on the *spinal cord*.—Chloral hydrate, mephenesin and bromides.
- (iii) By acting on the *motor nerve endings*.—Curare, conium and magnesium.
- (iv) By acting on the *muscles directly*.—Quinine, nicotine and coniine.

3. **Drugs increasing the activity of the plain (involuntary) muscles :**

- (i) By acting on the *autonomic ganglia*.—Nicotine.
- (ii) By acting on the *peripheral nerve endings* either *cholinergic* (acetylcholine, physostigmine, neostigmine, pilocarpine and colchicine) or *sympathomimetic* (adrenaline, ephedrine and amphetamine) acting on the plain muscles of the gastro-intestinal tract, bronchi, gall-bladder, urinary bladder, uterus, capsule of the spleen and the iris, including various sphincters and blood vessels according to their respective innervations : also morphine group.
- (iii) By acting *directly* on the *muscles*.—Posterior pituitary extract, histamine, lead and barium.

4. **Drugs decreasing the activity of the plain (involuntary) muscles :**

These are also called *antispasmodics* and have a wide field of clinical use.

- (i) By acting on the *autonomic ganglia*.—Nicotine, lobeline, gelseminine and coniine. Of those lobeline only is of clinical importance.
- (ii) By acting on the *peripheral nerve endings*.—Atropine group, papaverine group, pethidine (action is partly direct on the muscles) and adrenaline group acting according to the respective type of innervation.
- (iii) By acting *directly* on the *muscles*.—Nitrites, papaverine, benzyl benzoate, pethidine and caffeine group.

Drugs Acting on the Pupil

The pupil contains two sets of muscle fibres, one is *circular*, which on contraction, *constricts* the pupil and the other one is *radial* and *dilates* the same. The normal size of the pupil is the mean of the activity of these two sets.

There are also two sets of nerve fibres. The first set is the autonomic fibres of the *third nerve*. These have the (a) centre in the floor of the aqueduct of Sylvius, (b) a relay in the ciliary ganglion and (c) termination in the circular muscles of the iris. The second set probably has a (d) centre in the medulla, comes out from the *superior cervical ganglion* through the 2nd, 3rd and the 4th dorsal nerves and (e) ends in the radial muscle fibres. (See fig. 37).

The size of the pupil is mostly controlled by the third nerve system. The stimulation of the centre causes constriction : its inhibition as from an impulse from the superior psychic

centre such as a strong emotion causes dilatation of the pupil. The peripheral ends may be stimulated or depressed.

The pupil is dilated either by the paralysis of the same or the stimulation of the cervical sympathetic system. In excitement or fear and in asphyxia, the suprarenal secretion is probably increased which causes sympathetic stimulation and dilatation of the pupil. The drugs used as the pupil dilators are called the **mydriatics** and the constrictors, the **myotics**.

1. **Mydriatics** or pupil dilator drugs act as follows :

- (i) By *paralysing* the 3rd nerve-endings.—Atropine, homatropine, hyoscyamine and hyoscine.
- (ii) By *paralysing* the ciliary ganglia.—Gelseminine, curare and sparteine ; also later stages of nicotine, coniine and lobeline poisoning.
- (iii) By *depressing* the 3rd nerve centre.—Asphyxia, 2nd stage and 4th plane of 3rd stage of anæsthesia and hypnosis.
- (iv) By *stimulating* cervical sympathetic endings.—Cocaine, adrenaline, ephedrine and amphetamine.

LACHESINE HYDROCHLORIDE (Not official).—A synthetic preparation, acts as *mydriatic* and *cycloplegic*, the intensity and duration of action being intermediate between homatropine and atropine and is used in 1% solution especially in persons sensitive to atropine group when atropine is causing irritation of the conjunctiva and the eye-lids.

2. **Myotics** (G. *myein*, shut) or pupil-contracting drugs are as follows :

- (i) By *stimulating* the 3rd nerve centre.—Opium, early 3rd stage of general anæsthesia and moderate dose of hypnotics.
- (ii) By *stimulating* the ciliary ganglia.—Moderate dose of nicotine, coniine and lobeline, but in a big dose, the pupil is dilated by paralysing the ganglia.
- (iii) By *stimulating* (the parasympathetic) 3rd nerve-endings.—Acetylcholine, carbachol, physostigmine, neostigmine, pilocarpine and muscarine.
- (iv) By *stimulating* directly the iris muscles.—Ergotoxine.

In the usual practice, atropine, homatropine, hyoscine, cocaine and adrenaline are used as *mydriatic* and physostigmine, neostigmine and pilocarpine as *myotic*.

The site of the action may be localised as follows :

(i) If it is *local*, the drug acts soon after the application even when the blood vessels are ligatured or the eyeball is excised. If applied on one eye or on a portion of the pupil, only that part is affected.

(ii) If it takes some time to act and acts bilaterally when applied to one eye or from systemic administration but does not act when the blood vessels are ligatured, the action is *central*.

INTRA-OCULAR TENSION.—This is *lowered* by physostigmine and pilocarpine and *increased* by atropine, homatropine, hyoscyamine and hyoscine.

ACCOMMODATION

The ciliary muscles are responsible for accommodation. Both the sympathetic and the parasympathetic activators interfere with balanced contraction or relaxation of these muscles. The *sympathetics* (and especially the parasympathetic inhibitors) cause paralysis of the near and the *parasympathetics* mainly of the distant vision.

So accommodation is paralysed or impaired by Atropine, Homatropine, Hyoscyamine, Hyoscine, Physostigmine, Pilocarpine, Gelseminine, Coniine and Cocaine.

XI. DRUGS ACTING ON THE CARDIO-VASCULAR SYSTEM

The Cardio-vascular system consists of :

- (i) The *muscles* of the heart : also the *excito-motor apparatus* in the nodes, their connections and in the bundles.
- (ii) The coronary *blood-vessels*.
- (iii) The *innervation* by the vagus (the cardio-inhibitor) and the sympathetic (the cardiac accelerator), with centres in the medulla and terminations in the genetic or impulse producing tissues of the heart.

The *vagal stimulation* causes slowing of the heart beat, depression of the force of both the auricular and ventricular contractions and also of the auriculo-ventricular conduction. The duration of the systole and so of the refractory period is shortened and the blood pressure falls. The coronary blood vessels are constricted. The vagal control is best marked in the young adult : it is less so in the two extremes of life. The transmission of the vagal impulse in the heart as elsewhere, is through a chemical agent, acetylcholine.

The *sympathetic stimulation* causes quickening of the heart beat, increase of the force of contraction, increased auriculo-ventricular conduction, rise of blood pressure and dilatation of the coronary blood vessels.

The vagus exercises a tonic control over the heart. The sympathetics have no constant action but are excited by a sudden emotional disturbance, reflex stimulus or by an outpouring of the suprarenal secretions.

The *blood pressure* is controlled by the carotid sinus. A rise in pressure causes stimulation of the vagal centre and bradycardia. A fall inhibits the vagal and consequently stimulates the cardioacceleratory and vaso-motor centres and increases the suprarenal activity.

The *force* of the cardiac contraction also depends on the tonicity or tension of the chambers and the oxygen supply. An adequate return of the venous blood to the right auricle is essential. This distends the chambers, inhibits the vagal centre, (Brainbridge reflex) and increases the force of cardiac contraction. The stretched heart muscles containing a large volume of blood in the different chambers therefore, contract more efficiently and blood supply into the arterial system improves.

Oxygen supplied through blood in the coronary arteries is also essential for effective cardiac contraction. Food, both carbohydrate and protein, can be utilized only in the presence of O_2 . Anoxæmia tends to accumulate lactic acid, increases the frequency of the heart beat which, if great, lowers the cardiac output. During a period of violent muscular exertion, 1/15th of the total blood passes through the coronary circulation and

total oxygen consumption is 1/5th of the whole body. But during rest it is much lower but yet much greater than that of any other tissue.

So, an effective venous return to the chambers, its timely emptying with adequate force into the arterial system raising the aortic pressure sufficiently to ensure proper coronary filling, free supply of oxygen and also of glucose and balanced protein and salt concentration are essential for the optimum activity of the heart.

Pathological conditions, as lesions in the heart muscles and the valves, failure of the vaso-motor system and presence of an abnormal rhythm which interferes with the normal blood flow require various therapeutic measures.

The *vagal centre* is excited by drugs acting as general medullary stimulant. But the *sympathetic centre* is excited reflexly by an afferent impulse from a cutaneous stimulation (as counter-irritation), gastric irritation (as by alcohol), deficient oxygenation, excitement or by drugs of the adrenaline group. Vagal depressants as atropine increase the sympathetic activity.

Certain drugs mainly act in the heart muscles but most of these have other actions also.

In tabulating the actions of different drugs of this group, it must be understood that in none, this is absolutely selective limited to either the heart muscles, the nerves or the blood-vessels. So it is more convenient to classify these according to the effects produced by them on the circulation as a whole.

DRUGS ACTING ON THE HEART

The sites of action may be (i) on the contracting *muscles* of the heart : (ii) on the *genetic tissues*, producing and conducting impulses or/and (iii) *autonomic nervous mechanism*, sympathetic and vagus (in the medullary centre, ganglia or in the peripheral terminations).

A. DRUGS THAT SLOW THE HEART RATE

(1) By direct action on the *heart muscles*.—

This is mainly by drugs of digitalis group also by benzedrine, strychnine, posterior pituitary extract, quinidine, chloral hydrate, aconitine, potassium and magnesium ions.

(2) By action on any part of *vagal mechanism*.—

(i) *Medulla*.—(a) By raised *blood pressure* through carotid sinus as by leptazol, nikethamide, strychnine, benzedrine and for a short period by adrenaline, ephedrine and caffeine.

(b) By acting on the *vagal centre* as carbon dioxide, a general anæsthetic in the early third stage, morphine, aconitine, digitalis group and strychnine.

(c) *Reflexly* through a profound peripheral stimulus as severe burn, inhalation of an irritant gas as ammonia, (5th and 10th nerve reflex) or a big oral dose of concentrated alcohol.

(ii) *Intracardiac ganglia*.—Nicotine, lobeline, gelseminine and coniine in early stage.

(iii) *Vagal nerve-endings*.—Acetylcholine group, physostigmine and pilocarpine.

(a) Some of these **increase the cardiac output** also and are used therapeutically. These are the digitalis group, suprarenal extract, leptazol, nikethamide, benzedrine, ephedrine, posterior pituitary extract, strychnine and ammonia (by inhalation): also quinidine in auricular fibrillation.

(b) Drugs that slow the pulse-rate but **do not increase the output** include physostigmine, pilocarpine, choline, aconitine, veratrine, lobeline, hydrocyanic acid, acetanilide, phenacetin, phenazone, emetine and chloral hydrate also a potassium salt intravenously.

B. DRUGS THAT ACCELERATE THE HEART RATE

These act (a) by stimulating the *cardio-accelerator mechanism* directly as by adrenaline also ephedrine, cocaine, benzedrine and reflexly by moderately strong peripheral stimulus (a small dose of alcohol by mouth or moderate degree of skin irritation).

(b) Depression of the *vagal mechanism* in the centre by lowered blood pressure also anoxæmia, profound anæsthesia and narcosis; in the *ganglia* by nicotine group and in the *peripheral endings* by atropine group.

(c) Action on the excito-motor (*pace maker*) system as by caffeine group.

(d) *Toxic* dose of digitalis, aconite, quinine and coal-tar antipyretics.

(i) Those that in addition **increase the force of the heart beat** include alcohol, chloroform, ether, camphor, (also most other volatile oils), leptazol, nikethamide, benzedrine, caffeine, suprarenal extract, ephedrine, cocaine and the atropine group; also calcium chloride intravenously.

(ii) Those that **diminish the force** include nicotine, coniine, lobeline and gelseminine; also diminished O_2 and increase of CO_2 in the blood (anoxæmia) and repeated doses of posterior pituitary extract and ephedrine.

CARDIAC STIMULANTS include drugs that improve the circulation when this is deficient as in various types of heart failure. These (a) in an acute condition as in sudden syncope, are drugs that quickly accelerate the heart with increase of output. (b) Digitalis group by acting on the heart increases the force of contraction also the cardiac output and consequently is a cardiac stimulant although in a different way but acts more slowly.

The heart and respiratory failures are often combined and respiratory stimulants as oxygen-carbon dioxide mixture, strychnine, caffeine, leptazol, nikethamide, camphor, ephedrine and benzedrine act as cardiac stimulant also.

These are thus called *analeptics* or restoratives of cardiac deficiencies.

C. DRUGS ACTING ON THE BLOOD-VESSELS

The blood-vessels in health are moderately contracted (*tonicity*) which is helpful in maintaining a continuous blood flow: these dilate only under certain circumstances by inhibiting the contracting influence. This tonic contraction is controlled by vaso-motor system with its centre in the medulla.

The smaller arterioles with proportionately greater musculature are mainly affected by these drugs; the bigger arteries, veins or the capillaries are comparatively little affected.

(1) Vaso-dilators

(a) All irritants *locally applied*, cause dilatation of the blood vessels (vaso-dilators). These are either rubefacient, vesicant or caustic and have already been described. (See p. 111).

(b) But other drugs cause vaso-dilatation by their *systemic action*. These are, the nitrites, papaverine, acetylcholine group, the caffeine group (by action on the muscles); alcohol, chloroform, ether, chloral group and coal tar antipyretics (by depressing the vaso-motor centre); opium alkaloids (undetermined central action) and thyroxine; also toxic doses of nicotine, lobeline, and ergotoxine.

CAPILLARY DILATORS.—The most important is *histamine*. With a momentary rise, the blood pressure markedly falls on account of capillary stasis. But for its many side actions this cannot be very much used.

Arsenic and *antimony* are also capillary dilators. In minute doses, these are utilised to improve the cutaneous circulation and nourishment (prescribed in many skin affections) but in big doses, these act as capillary poison with considerable fall in blood pressure and favouring transudation of fluid into the cellular spaces especially of the bowels and the lungs, these cause watery diarrhoea and œdema of the bases of the lungs.

Although the capillaries have no muscular wall, they maintain a certain degree of tone and have a sympathetic nerve supply. The normal circulation is dependent on this tone.

(2) Vasoconstrictors

(i) Those *acting locally*, are application of cold, suprarenal extract, ephedrine, benzedrine, oil of turpentine, solution of heavy metals as of silver, lead and of aluminium and dilute sulphuric acid.

(ii) Those *acting after absorption* are suprarenal extract, posterior pituitary extract, strychnine, CO₂, digitalis group,

ergot, hydrastis, physostigmine, pilocarpine, turpentine, ammonia, barium chloride and muscarine. Their mode of action is as follows :

(a) Stimulation of the *medullary centre*, reflexly by moderately powerful skin irritants : asphyxia (CO_2 stimulation) : drugs as strychnine, pictrotoxin, benzedrine, caffeine, ammonia, atropine, cocaine, hydrastine and momentarily by aconitine and hydrocyanic acid.

(b) Direct action on the *vessel wall*.—Acting on the nerve-endings as adrenaline, ephedrine, benzedrine, ergotoxine : acting on the muscle as pituitary extract, also toxic doses of digitalis, barium and veratrine.

Nicotine, coniine, and lobeline cause transient vaso-constriction by stimulating the sympathetic ganglia.

These effects are best shown on the splanchnic blood vessels, richly supplied with nerves and muscles : least on those of the lungs and the brain which are poor in muscles and nerve. The blood-vessels of the limbs show intermediate effect. The bigger blood-vessels containing less muscles and more fibrous tissue are not as much affected.

The results of vaso-constriction are the rise of blood-pressure, medullary stimulation (pulse slowed and respiration quickened), increased urination and congestion of the lungs and the brain.

PRIVINE, a synthetic vasoconstrictor, supplied in 10 c.c. phials is used in rhinitis : this with cibazol 5% is useful in acute and chronic naso-pharyngeal infections.

BLOOD PRESSURE

Arterial blood pressure depends on (a) the *cardiac output* and the *resistance* offered by the arterial wall : these are under control of the medulla (the vagus and the vaso-motor centres) : (b) these centres again are operated by reflexes from the *carotid sinus*. Rise of pressure in the sinus causes slowing of the heart and dilatation of the blood vessels and a fall in pressure has the opposite effect (Heymans). The vagal centre is further regulated by sensory impulses from the auricles and aortic arch. (c) Certain *diseased conditions* alter the blood pressure operating through the heart muscles, blood volume, arterioles directly and through the medullary centres. (d) Certain *drugs* and *asphyxia* also disturb the blood pressure.

(i) **Blood pressure is raised by** (a) *Medullary Stimulants* as amphetamine, caffeine, strychnine, leptazol, nikethamide, camphor, atropine, CO_2 , cocaine and to some extent digitalis.

(b) *Sympathetic ganglia* stimulants : nicotine, lobeline and coniine (temporary).

(c) *Sympathetic nerve endings* ; adrenaline, ephedrine, amphetamine and ergotoxine (in small doses).

(d) *Arterial wall* directly : posterior pituitary extract, barium and digitalis (in toxic doses).

(e) *Direct cardiac action* by digitalis group when the pressure is lowered by feeble myocardiac action. *Reflex stimulants* as alcohol or a counterirritation causes a temporary rise in pressure.

(ii) **Blood pressure** is lowered by (a) *medullary depressants* as an over-dose of general anæsthetics, hypnotics, narcotics and coaltar analgesics. (b) *Vaso-dilators* and *capillary dilators* (See p. 636). (c) Lessening of *blood volume* as by hæmorrhage, vomiting and diarrhœa and (d) *shock* and (e) a *direct cardiac depressant* as potassium cyanide.

(3) Sclerosing Agents

Certain drugs given intravenously may cause local damage to the intima resulting in their sclerosing obliteration. These are therapeutically used for the treatment of piles and varicose veins.

Drugs in common use now are quinine and urethane (p. 343) and ethanolamine.

Others formerly in use were carbolic acid (p. 168) and sodium morrhuate (p. 286) solutions.

ÆTHANOLAMINA (*Æthanolamin.*), $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$

Ethanolamine is β -aminoethanol, prepared by the action of ammonia on ethylene oxide. It contains not less than 96% of $\text{C}_2\text{H}_7\text{ON}$.

A clear colourless or pale yellow inodorous liquid soluble in water and in alcohol 90%, slightly soluble in solvent ether, benzene and in light petroleum.

Injectio Æthanolaminæ Oleatis (*Inj. Æthanolamin. Oleat.*), See p. 42.

Dose, 30 to 75 minims or 2 to 5 ml. intravenously as a sclerosing agent.

Ethanolamine oleate is used intravenously for the treatment of piles and varicose veins. A portion of the vein is isolated and oleate of ethanolamine 2 to 5 c.c. being divided into 3 or 4 portions is injected at different sites and the fluid is held up for some time. The treatment is repeated *after one week* till the varices are completely obliterated. The injection is painless, a little escape into the subcutaneous tissue is not particularly harmful and the sclerosing effect is quite good. The intima of the vein is destroyed causing fibrotic obliteration of the vein.

When thrombosis of the deep veins of the leg, acute phlebitis or other affections are present near the varices, this treatment is contraindicated.

Available in 2 c.c. and 5 c.c. ampoules and 20 c.c. vials.

(4) Styptics

Styptics or hæmostatics are drugs that control bleeding and those having *local action* on the blood vessels are more suitable for therapeutic purposes.

(a) Application of *adrenaline* solution also of *ice* cause direct contraction of the walls of the blood-vessels.

(b) Coagulants of albuminous matter cause the same effect by forming a coagulum round a blood vessel. These are, *tannic acid* and all preparations containing it, *salts of heavy metals* as silver, lead, copper, zinc, aluminium, iron and also of *bismuth*.

(c) Certain substances as *oxidised cellulose*, *fibrin foam*, *gelatin sponge* and *calcium alginate* applied locally, are effective hæmostatics. But oxidised cellulose is markedly acid and inactivates antibiotics and thrombin; fibrin foam is difficult to sterilize and the use is complicated. Gelatin sponge can be sterilised by heat, inexpensive, non-irritant and does not inactivate antibiotics or thrombin. It is useful in visceral surgery: calcium alginate gauze can be sterilized by autoclaving and is very suitable.

Sodium alginate is used to arrest bleeding: applied in solution on a raw tissue surface, it reacts with calcium in the serum to cause precipitation of calcium alginate which is styptic: it may also be applied as powder or gauze and sprayed with isotonic calcium chloride solution.

Calcium alginate gauze or pads are slowly and completely absorbed by body tissues.

(d) Those acting *after absorption* have the disadvantage of raising the systemic blood pressure and are therefore unsuitable for internal bleeding. Some of these are used to control the uterine bleeding and in addition to the blood vessels, the muscles of the uterus get into tonic contraction which effectively stops bleeding. *Ergot*, *hydrastis*, *posterior pituitary* and *suprarenal extracts* are often used for this purpose.

(5) Coagulants and Anticoagulants

Those *hastening blood coagulation* in a case of hæmorrhage are calcium preparations (p. 272), heavy metals (p. 428), blood platelets, brain or spinal cord extract, congo red (p. 177), vitamin K (p. 289) and viper venom.

THROMBOPLASTIN, said to contain blood platelets, blood and tissue cell extracts, liberates prothrombin which with calcium ion causes coagulation of blood. This applied locally or injected subcutaneously or intramuscularly, stop capillary hæmorrhage.

Coagulen-Ciba (obtained from bovine blood-platelets) in 3% solution (Dose up to 20 ml.) is used locally, orally (3 to 5 g. powder dissolved in 200 c.c. of water), subcutaneously or intramuscularly (5 to 20 c.c.) and intravenously (3 to 10 c.c. very slowly). *Hemoplastin P.D.* (containing prothrombin and thrombokinase), Dose, 2 ml. is frequently used

intramuscularly. *Thrombin* (topical) available as sterile powder with a sterile saline diluent, used to control superficial capillary hæmorrhage.

TOLUIDINE BLUE (See p. 177), has been recently reported to be of value in thrombopenic purpura also is a corrective of overaction of heparin.

RUSSELL'S VIPER VENOM.—This is highly coagulant and a sterile solution of 1 in 10,000, locally applied, is sufficient to stop capillary oozing. It is especially useful in hæmophilia. The Indian variety is better. It is not toxic in such dilution.

VENENUM VIPERÆ, Daboia Venom, *Ind. Pharm. List* is used locally in 10,000 solution and intramuscularly (1 to 3 mouse units : 30 mouse unit is 1 mg.) as hæmostatic.

Those *delaying coagulation* are citrates, dicoumarol, heparin and hirudin also intravenous injection of peptone : of these the first three have therapeutic uses.

HEPARINUM (*Heparin*.)

Heparin is the sterile preparation of sodium salt of a complex organic acid present in mammalian tissue especially in *lung* and *liver* which delays the clotting of *shed* blood. It contains not less than 75 units per mg. : one unit is 0.0077 mg. of the standard.

A moderately hygroscopic greyish brown powder completely soluble in water and in saline solution forming a clear colourless or straw-coloured fluid.

Dose by intravenous injection, 6,000 to 12,000 units.

Injectio Heparini is a sterile solution of Heparin in injection of sodium chloride, containing between 90 to 110% of the labelled amount of heparin.

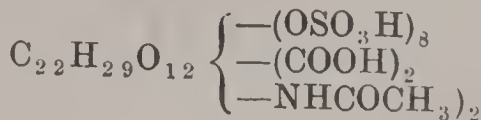
A clear, colourless or straw-coloured fluid transparent without any deposit.

Dose as of Heparin.

Pharmacology [and Therapeutics]

In 1916, Howell and his collaborators isolated from the liver a powerful anticoagulant substance which was consequently named *heparin*. Later on, it was found to be present in many tissues throughout the body and especially in the lungs. Chemically it is a *mucoitin polysulphuric acid* in which the basic tetrasaccharide unit has five sulphuric ester groupings.

The original preparation was purified and standardised by Howell (1928) so that 1 mg. would prevent coagulation of 100 c.c. of blood. This is further improved now and 0.01 mg. of the crystalline barium salt is *one unit* and one mg. prevents coagulation of 500 c.c. of cold cat's blood for 24 hours (Toronto unit).



Heparin is strongly acidic and probably acts by forming a complex with a factor present in soluble fraction of serum albumin and acts as anticoagulant by inactivating thrombin. This heparin-serum albumin fraction (a) prevents conversion of prothrombin into thrombin, (b) is antagonising the action of thrombin itself to convert fibrinogen into fibrin (Quick, 1944) and (c) is preventing agglutination of the blood platelets.

The common factor appears to be a strongly *negative electric charge* carried by the blood protein caused by its combination with heparin anion.

(i) Heparin is used in the *laboratory* to keep up blood in fluid state and this does not interfere with cell counting and biochemical examinations. The white cells should be counted without much delay.

Hæmocrit examination may be correctly made but not hæmolytic test, sedimentation test and serological examination.

(ii) Heparin is more useful in **blood-transfusion**. Either the blood taken out is treated with heparin or the donor is heparinised, usually 60 mg. in a single injection is given.

One mg. of heparin per kilo body weight intravenously raises the coagulation time of blood, after an interval of 10 minutes, to 40 minutes. As the effect passes off in 20 to 140 minutes, blood should be taken from the donor 10 minutes after the administration of heparin. This is harmless both to the donor and to the recipient.

(iii) Heparin is also used in **vascular surgery**, in **various thrombotic processes** as venous thrombosis after surgical operation especially decubitus thrombosis (thrombosis in the legs after child-birth) and pulmonary embolism : also in cavernous sinus thrombosis and in coronary thrombosis (probably heparin increases the coronary blood flow).

If the intravenous method is chosen, to maintain a coagulation time over 15 minutes, the injection is to be repeated every 4 to 6 hours.

As continuous drip, 10 mg. in 100 ml. of normal saline is given at the rate of one to two ml. per minute. No cumulative effect is produced and a two to four times increase in coagulation time may be maintained.

In order to prolong the action, special preparations have come into use. (a) Heparin (100 mg./ml.) in Pitkin's menstruum (18% gelatin, 8% glucose, 1% acetic acid in sterilised water) may be given subcutaneously : the action starts in two hours, the maximum effect is in 15 hours and total duration of action is 40 hours.

Heparin Pitkin Menstruum Warner (300 mg. in 3 ml.) also *Heparin Retard* 2 c.c. ampoule of 20,000 i.u. are available.

(b) An aqueous emulsion of heparin (200 to 300 mg./ml.) in a menstruum of a cholesterol derivative 33%, peanut oil 65% and bees wax 2%. A single intramuscular injection prolongs coagulation upto 24 hours.

The sensitivity to heparin varies : this may be tested by a preliminary intravenous injection of 10 mg.

Dose.—A dose of 150 mg. morning and night with 100 mg. once in the day : when the symptoms have subsided, 100 mg. twice daily have been considered adequate (Bauer, 1946). Heparin in Pitkin's menstruum in 200 to 400 mg. dose every 48 hours may do.

Heparin B.D.H. is available as 10 c.c. heparinised tubes containing 100 units for collecting blood samples and for use in transfusion, 500, 1000 and 5000 units per c.c. in 5 c.c. vials : also *Heparin* Boots, 1000 and 5000 i.u. per c.c.

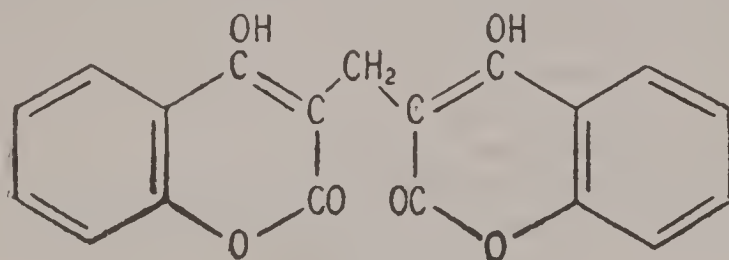
One unit is 0.01 mg. (Toronto) and 5 times stronger than Howel unit.

PROTAMINE SULPHATE 1%. 5 to 10 ml. intravenously quickly antagonizes the overaction of heparin. In other hæmorrhagic state 50 mg. in 5 ml. intramuscularly every 4 to 6 hours or 150 mg. in saline solution intravenously very slowly in one hour has been favourably reported on.

Also see *Toluidine Blue* p. 177.

DICOUMAROL (*Dicoumarol.*); Dicoumarin, $C_{19}H_{12}O_6$

Dicoumarol or dicoumarin is 3 : 3'-methylene : bis-4-hydroxycoumarin, prepared by action of formaldehyde on 4-hydroxycoumarin, obtained as its sodium derivative by metallic sodium acting on methyl acetyl-salicylate. It was first isolated by Link (1941) from spoiled sweet clover hay.



Dicoumarol

A white or creamy white microcrystalline powder with slight pleasant smell and bitter taste.

Dose, $\frac{3}{4}$ to 5 grain or 50 to 300 mg. daily.

Pharmacology [and Therapeutics]

Dicoumarol like heparin prolongs coagulation time of blood (a) probably by interfering with *vitamin K* activity (believed to act as a competitive inhibitor of vitamin K), and (b) by reducing adhesiveness of blood platelets which prevent thrombus formation also (c) by prolonging the clot-retraction time.

It differs from heparin being (a) slower in action requiring 24 to 48 hours for the full effect : (b) it has a more prolonged action : (c) not markedly cumulative : (d) capable of oral administration and (e) cheaper.

Increase of coagulation time indicates a depletion of prothrombin in the blood due to an inhibition of its formation in the liver. This effect only occurs *in vivo* and is without effect on shed blood. The drug takes about 12 to 72 hours to adequately lower the prothrombin level and this is the same both in oral and intravenous administration. After stopping the drug the normal blood condition is restored in 3 to 7 days. As there is no cumulative effects, this restoration is the same even after greatly prolonged treatment with large doses.

Dicoumarol is used in the treatment of various types of thrombosis and embolism and is of value as a prophylactic for prevention of postoperative complications.

(i) Postoperative and puerperal thrombosis also retinal and cerebral thrombosis occasionally coronary thrombosis and pulmonary embolism are successfully treated with dicoumarol.

(ii) As *prophylactic* against postoperative embolism and thrombosis, the initial dose is given 12 hours before the operation. In congestive heart failure, dicoumarol tends to lessen the incidence of embolism.

A depletion of prothrombin level to between 10 to 30% of normal is usually necessary and upto this is safe. If below 10%, spontaneous bleeding is very liable to occur.

Detailed animal studies have shown that the drug has no effect on the hepatic function and on composition of urine, blood sugar, red and white cells count, bilirubin and calcium and nonprotein nitrogen in the blood also icteric index and fragility of red cells and on blood platelets. But prothrombin level must be watched and should not be allowed to fall too low.

MODE OF ADMINISTRATION.—For *prompt action* heparin is given first and the effect is kept up with dicoumarol. But in most cases dicoumarol only may do.

(i) The *initial dose* of 300 to 350 mg. ($4\frac{1}{2}$ to 5 gr.) is given orally, in divided doses to prevent gastric irritation followed by 100 mg. ($1\frac{1}{2}$ gr.) daily as the maintenance dose; the intensity of action is regulated by prothrombin estimation.

(ii) Or after the initial dose of 200 to 300 mg. (3 to $4\frac{1}{2}$ gr.), 200 mg. (3 gr.) is given on the second day. If on the 3rd day the prothrombin level is below 20% of normal, the drug is temporarily withheld: if not, another dose of 200 mg. is given.

Recent introduction of Heparin-Pitkin menstruum causing slow absorption and prolonged action of heparin has made it possible to have the desired effect more precisely with a standardised dose of heparin (dicoumarol dose tends to vary from case to case) and this may be controlled by a simple coagulogram at bedside without daily prothrombin estimation in the laboratory.

CONTRAINDICATED.—(a) *Kidney disease* with deficient urinary secretion and also *liver diseases*: (b) existing prothrombin and vitamin K deficiency, (c) subacute bacterial endocarditis and heart disease with gross myocardial deficiency, (d) conditions of actual and potential bleeding and (e) an acute febrile condition.

PRECAUTIONS.—(a) The coagulation time and prothrombin level should be watched: (b) if bleeding is severe, the drug is stopped and a transfusion of 300 to 500 ml. of blood plasma is given also vitamin K: Protamine sulphate and toluidine blue are also helpful. (c) If vitamin C deficiency is present, this vitamin should be given from the beginning: (d) if the temperature is high, this should be carefully watched.

COMMERCIAL PREPARATION.—TEMPARIN in 50 mg. ($\frac{3}{4}$ gr.) tablets is available.

SUMMARY.—As *anticoagulant*, *heparin* has been used intravenously in vascular surgery, blood transfusion and for prevention and treatment of acute thrombosis and embolism: the action is rapid but short staying. The effects are maintained with *dicoumarol* orally or by heparin in Pitkin's menstruum subcutaneously: the intensity of action is watched for by examining the coagulation time (to be kept near to 15 minutes).

Dicoumarol orally acts slowly and this action persists fairly long. This is suitable in chronic cases, may be started after heparin. The prothrombin level is to be daily watched for which should be near to 30% of normal.

Overaction is counteracted by vitamin K, blood transfusion and by protamine sulphate.

TROMEXAN, Bis-3-3'-(4-oxycoumarinyl) ethyl acetate. Not official, has been found to have about $\frac{1}{4}$ th toxicity and potency of dicoumarol with action developing and passing off more quickly. It is well tolerated orally and readily absorbed.

With initial daily dose of 1200 mg. (in 4, 300 mg. tablets) in 24 hours the effect appears in 3 hours reaching maximum in 12 to 24 hours prothrombin level falling below 50% ; after 2 to 3 days, the maintenance dose is 300 to 600 mg. daily. Prothrombin level is estimated daily and when stabilised at 20% the maintenance treatment is undertaken.

If prothrombin estimation is not possible, 3 tablets are given on the first, 2 to 3 tablets on the 2nd, 2 on the 3rd, 1 to 2 on the 4th and 1 tablet daily afterwards. This is fairly satisfactory in a case of average severity. Appearance of red blood cells in the urine indicates overaction.

Digitalis Group

This includes several drugs such as *digitalis purpurea*, *digitalis lanata*, *ouabain*, *urinea scilla*, *convallaria majalis*, *apocynum cannabinum*, *helleboras nigar* and *adonis vernalis*. The active principles are powerful glycosides.

DIGITALIS FOLIUM (*Digit. Fol.*), Digitalis leaf, Foxglove leaf

The earliest record for therapeutic use of digitalis is in *London Pharmacopæia* (1650) for tuberculosis and as an emetic. Withering (1785) used it as a diuretic for dropsy which was found to be due to circulatory effects (Ferriar, 1799). By about 1860, it was considered to be a cardiac tonic and later on, Mackenzie used it in auricular fibrillation.

The leaves are collected from *Digitalis purpurea* when the plant is flowering. These are broadly ovate or lanceolate, 10 to 30 cm. long 4 to 10 cm. broad and terminate into winged stalks. The upper surface is dull-green and has short hairs and the under-surface is more densely hairy. The mid-rib is prominent and lateral veins leave it at acute angles. The margins are crenate, serrated or occasionally dentated and hard. The apex is subacute. These are rapidly dried at a low temperature (60°C) and stocked in an air-tight container in a dry place. All parts of the leaves are used in the form of powder or tablets. Has a slight odour and bitter taste.

It grows in India in the Nilgiris, Darjeeling and in Kashmere forests.

The Kashmere leaves make adequately powerful tincture. The imported leaves deteriorate rapidly in the tropics in spite of careful storage. Prepared tablets keep well.

Both the leaves and the seeds contain active *glycosides* : those of the former are more important.

The isolation of the glycosides in pure form is difficult. Three glycosides, *digitoxin* ($C_{41}H_{64}O_{13}$), *gitoxin* ($C_{41}H_{64}O_{14}$) and *gitalin* ($C_{35}H_{56}O_{12}$) have been isolated in stable form. Digitoxin is soluble in chloroform and alcohol but relatively insoluble in water. Infusion of the leaves, however, contains digitoxin, saponin present making a colloidal solution. Gitoxin in pure state is also insoluble in water.

These glycosides are usually present with *saponins*. The saponins have no specific action on the heart ; these in the digitalis group are *digitonin* and *gitonin* ; these increase solubility of the cardiac glycosides, but may cause gastro-intestinal irritation.

Each glycoside is a combination of an *aglycone* or *genin* with one or more molecules of *sugar*. The aglycone is the real active substance and sugars probably regulate water-solubility, cell penetrability and continuation of cardiac action (therapeutic potency) although these are themselves inactive.

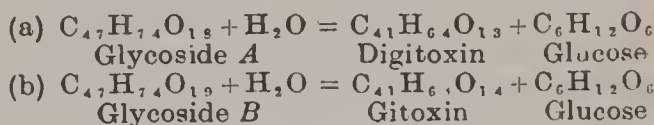
These aglycones have 23 carbon atoms but differences is mainly in the number, arrangement and function of the oxygen atoms.

Aglycones are chemically related to bile acid, cholesterol, sterols and sex hormones. The basic structure is a cyclopenteneph-nanthene nucleus to which is attached a lactone ring.

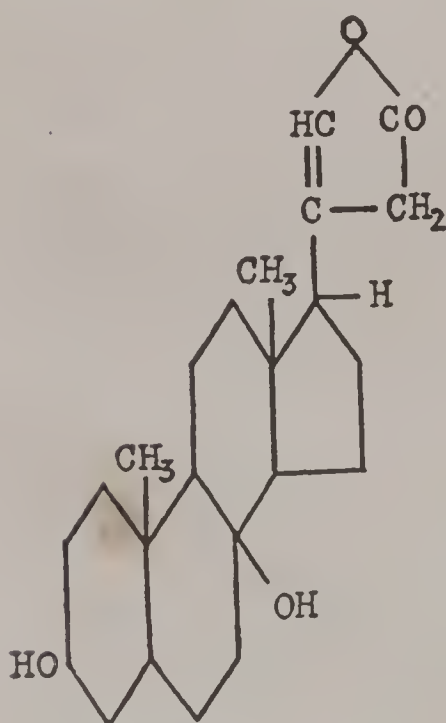
DISTRIBUTION OF CARDIAC GLYCOSIDES.—These are present in *digitalis* leaves and seeds : in *strophanthus* seeds : in *ouabain*, wood and bark, in *squill* bulbs and in *convallaria* flowers.

The glycoside of the seeds, *digitalinum verum*, (Kiliani) like others is insoluble in water but saponins keep it in colloidal suspension. These are readily decomposed, specially in acid solution. The leaves also contain tannin, colouring matter, volatile oil, sugar, starch, vegetable acids etc.

(i) Recent observations by Stoll and Kreis showed that *purpurea glycosides* are divided into two, *A* and *B*.

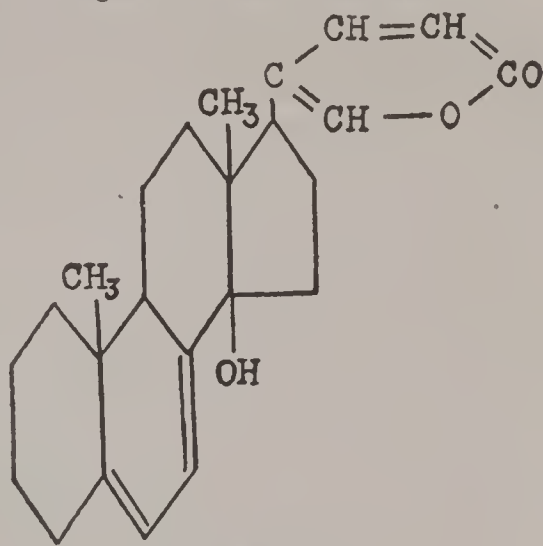


These are obtained from leaves and aglycone for (a) is digitoxigenin and for (b), gitoxigenin and gitaligenin. The seed glycoside, digitalin is less important.



Digitoxigenin

Digilanid A—(glucose and acetyl)=
digitoxin and aglycone, digitoxigenin.
Digilanid B—(glucose and acetyl)=
gitoxin and aglycone, gitoxigenin.
Digilanid C—(glucose and acetyl)=
digoxin and aglycone, digoxigenin.



Scillaridin A

(ii) The *lanata glycosides* are three : these are digilanid A (47%), digilanid B (16%) and digilanid C (37%). These have the aglycones, sugar and acetic acid.

Strophanthus gratus has the glycoside ouabain ($C_{29}H_{44}O_{12}$), sugar, rhamnose and aglycone, ouabagenin.

S. Kombé.—Glycosides are strophanthin and strophanthoside: sugars, glucose and cymarose and the aglycone, strophanthidin.

The chemical affinity is very obvious. Digitoxigenin ($C_{23}H_{34}O_4$), Gitoxigenin ($C_{23}H_{34}O_5$), Digoxigenin ($C_{23}H_{34}O_5$), Ouabagenin ($C_{23}H_{34}O_8$) and Strophanthidin ($C_{23}H_{32}O_6$).

Squill has glycoside, Scillaren A: sugar, glucose and rhamnose and aglycone, Scillaridin A.

INCOMPATIBLES.—Iron salts, lead acetate and cinchona. Glycosides are hydrolysed (made into glucose and other substances) by strong mineral acids, alkalies and digestive enzymes.

OFFICIAL PREPARATIONS.—DIGITALIS FOLII PULVIS (*Digit. Fol. Pulv.*), powdered digitalis leaf is green in colour. (i) *Digitalis Præparata* (*Digit. Præp.*), Digitalis leaves are made into a moderately coarse powder and biologically assayed. The strength is stated in terms of international standard digitalis powder, of which 80 mg. has the activity of one unit. For therapeutic administration, powdered digitalis must be adjusted to contain 10 units in 1 g. A green powder with slight odour and bitter taste. Dose, $\frac{1}{2}$ to $1\frac{1}{2}$ grains or 30 to 100 mg. (ii) *Tabellæ Digitalis Præparatæ* (*Tab. Digit. Præp.*), is prepared by moist granulation and compression. Each tablet if not otherwise stated is 1 gr. Strength is 10 units per gramme. Dose, as of powdered digitalis. (iii) *Tinctura Digitalis* (*Tinct. Digit.*), See p. 59. It contains in one mil or in 15 minims, one unit of activity. As it deteriorates on keeping, it should not be used after one year of its manufacture. Further, it loses its efficiency if long in contact with water as when dispensed in a mixture and therefore, digitalis should be added to it immediately before its administration. Dose, 5 to 15 minims or 0.3 to 1 ml.

DIGOXINUM, $C_{41}H_{64}O_{14}$, is a crystalline glycoside obtained from the leaves of *Digitalis lanata*: first isolated by Smith (1930).

Colourless and inodorous 4 to 5 sided tabular crystals with a bitter taste in dilute alcoholic solution. Almost insoluble in water but soluble in dilute alcohol.

The therapeutic activity of 1 mg. of digoxin is the equivalent of 300 mg. of prepared digitalis and 3 ml. (45 min.) of tincture of digitalis.

Dose, Oral: 1/60 to 1/40 grain or 1 to 1.5 mg initial and 1/240 grain or 0.25 mg. once or twice daily, maintenance dose. By intravenous injection, 1/120 to 1/60 grain or 0.5 to 1 mg.

OFFICIAL PREPARATIONS.—(i) *Injectio Digoxini* (*Inj. Digoxin.*), See p. 43. Dose, 150 to 300 min. or 10 to 20 ml. intravenously: (300 min. or 20 ml. contains 1/60 gr. or 1 mg. of Digoxin). (ii) *Tabellæ Digoxini* (*Tab. Digoxin.*), See p. 57. Digoxin content is between 90 to 110%. Dose as of Digoxin. Each tablet if not otherwise stated, contains 0.25 mg.

Pharmacology [and Therapeutics]

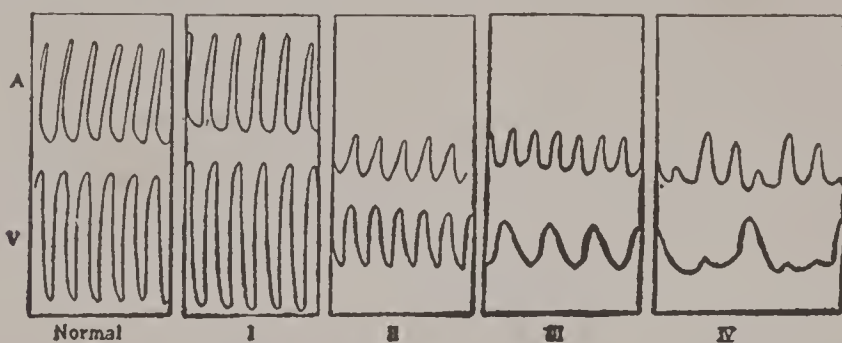
APPLIED EXTERNALLY, the glycosides of digitalis are irritant, especially to various mucous membranes. Some of them after an initial stimulation cause paralysis of the sensory nerve endings. But these have not much action on the intact skin. In pure state, these are insoluble in water and unstable for hypodermic administration. Further, such an injection is very

painful. Digoxin being more stable is suitable for injection intramuscularly or intravenously.

INTERNAL ADMINISTRATION.—There is one fluid preparation of digitalis for internal use, the *tincture*. This is dependable and often prescribed. The powdered *leaf tablets* are also used. *Digitoxin* is available as tablet or in ampoule for oral use or injection and getting popular.

Recently *digoxin* in tablet form orally and to a less extent its solution in ampoule intravenously is frequently used. This has all the three glycosides of digitalis lanata. Glycoside C is also used separately.

CARDIO-VASCULAR SYSTEM.—The experimental investigations of the action of digitalis with digitalis purpurea on the circulation have mostly been made on the isolated heart tissue or on the heart exposed inside the chest of an *animal*. The results obtained may not fully be the same as expected from its therapeutic administration in a human being. Further, the effect in *health* may not exactly be the same as in diseases.



(After Dixon)

Fig. 48.—The effects of an injection of digitalis into the dorsal lymph sac of a frog: Normal, before the injection. (I) After the injection: forcible systole and prolonged diastole. (II) Half an hour after: ventricles semi-contracted (imperfect diastole). (III) Fifteen minutes after: A-V block, 2 auricular contractions are followed by one ventricular. (IV) Auriculo-ventricular arrhythmia.

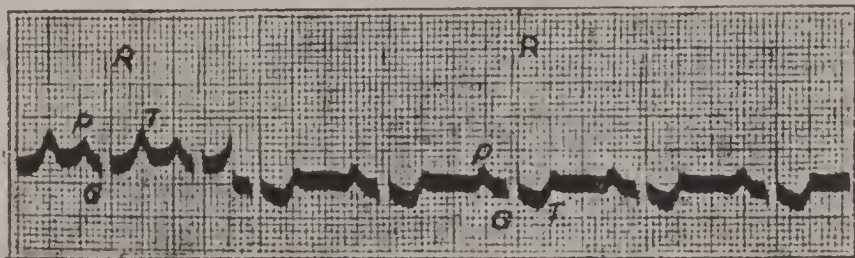
After absorption into the systemic circulation, digitalis mainly acts on the heart muscles. The glycosides probably enter into the protoplasm and split to release the active aglycones. These have some action on the medullary centre also.

1. The specific action of digitalis under experimental condition on a *frog's heart* is **DIRECT ON THE MUSCLES**. This in the beginning may be either on the impulse producing-conducting system or on the contracting system and often on the both. With a smaller dose, the **conductivity is depressed**, more of the auriculo-ventricular and less so of sino-auricular junction, so that an alternate auricular impulse may pass on to the ventricle: comparatively fewer impulses are transmitted from the sinus also. With a bigger dose the **force of contraction**

of both auricles and ventricles is soon increased including tonicity causing **diminished relaxation**. The muscle irritability is augmented. Imperfect diastole lessens filling up especially of the ventricles and the chambers become more and more contracted. So with a minimal lethal dose, auriculo-ventricular dissociation is more apparent which stops the ventricles in diastole ; with a bigger dose, the chambers are contracted and these stop in systole. The **inhibitory vagal mechanism** has very little action.

If an excised heart is perfused for some time with normal saline solution only, and it stops, adding a little digitalis to the fluid starts rhythmic contraction again showing an increase of excitability under digitalis.

2. But on a *healthy mammalian heart*, digitalis acts both on the **VAGAL MECHANISM*** and on the **HEART MUSCLES**. The inhibitory influence prolongs the diastolic period, lessens the



(Cushny)

Fig. 49.—An electrocardiogram, showing inverted T-wave in the second portion of the curve, taken after the administration of digitalis.

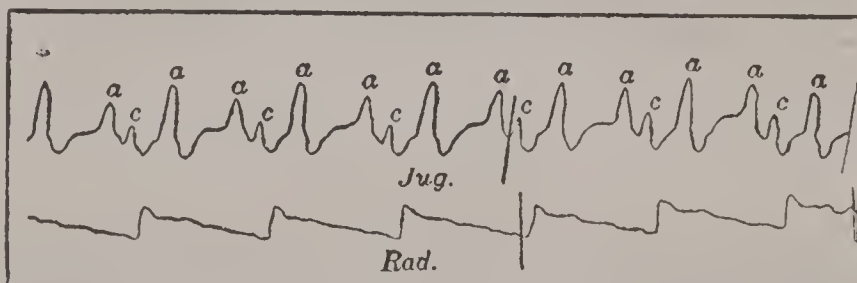
number of heart beats and increases the relaxation of the muscles ; muscular action tends to increase the excitability of the muscles and the force of the systole and to limit the relaxation. The resultant of these two actions is that the ventricular rate slightly comes down and the diastolic period is increased allowing better venous drainage. If the chambers are much dilated, these tend to contract and relaxation is lessened. In either case, *ventricles* are more completely filled up in diastole which contracting with greater force, increase the cardiac output. Longer diastole gives rest to the heart muscles. The *auricles* also act in the same way and the resultant of the inhibition and the muscular action is often contraction with greater force. The slowing of the rhythm is only moderate and increased output per beat more than counterbalances its effects ; on the whole a large volume of blood is driven into the aorta and the pulmonary artery. The **cardiac rhythm** is unaltered.

* The vagal action is probably reflex ; increased ventricular output stimulates carotico-aortic system (carotid sinus) and not as formerly believed due to direct stimulation of the medullary vagal centre (Heymans, 1932 and Weiss, 1938),

The **conduction** of impulses from the auricle to the ventricle may be moderately slower, from depression of the bundle by inhibitory activity. This is called the **FIRST STAGE** or the *Stage of Therapeutic Action*.

The electrocardiogram : T-wave is diminished in height and may even be inverted, often T_3 and occasionally T_1 and T_2 are involved. This is the earliest positive sign of digitalis action on the heart muscles. As the dose is increased RS-T segment is depressed and P-R interval increased but seldom exceeds 0.25 second. Atropine does not alter these effects.

If digitalis is given in a bigger dose, there is **excessive inhibitory activity** and less direct action on the cardiac muscles. The ventricles relax well during diastole and although the systole is still fairly powerful, the rate is made so slow that the total output of the heart per minute falls. The **rhythm** is slightly irregular also. Very often there is a certain amount of heart-block, from stimulation of the inhibitory mechanism, causing slight auricular dissociation so that some of the auricular impulses fail to reach the ventricles and the latter contract at a slower rate than the auricles occasionally sino-auricular block also appears. If the irritability of the ventricles is much increased, a spontaneous rhythm appears in the ventricles. The auricular contractions become much feebler. This is the **SECOND STAGE**.



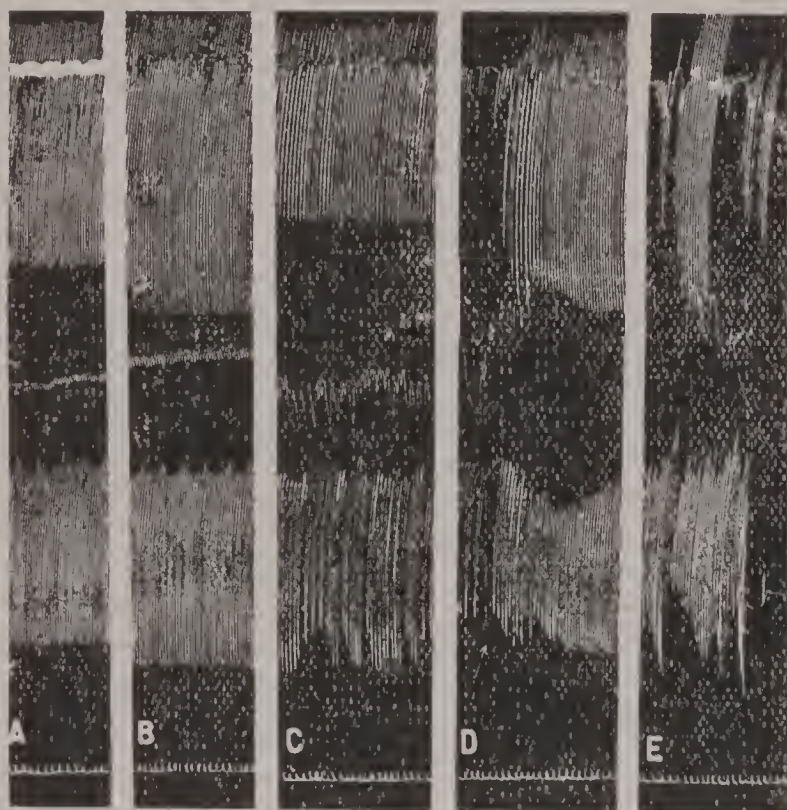
(After Mackenzie)

Fig. 50.—Overaction of digitalis ; every other auricular beat is responded to by the ventricle (depressed conductivity).

Duration of this stage is inconstant : may be short or even absent, depending on the activities of the inhibitory mechanism. These may be abolished by a preliminary injection of atropine.

When a very big quantity of digitalis is injected these two stages are short staying, especially the second stage. The ventricular rate is markedly accelerated due to **increased irritability of the heart muscles** which is not due to paralysis of the inhibitory mechanism and stimulation of vagus still lessens the rate and increases relaxation of the ventricle. The auricular rate is also markedly increased : there may be a difference in rhythm of the auricles and the ventricles causing periodic variations in the strength of the contractions of these chambers. The a-v conduction is impaired or lost due to direct action on the a-v bundle : rarely sino-auricular conduction is also impaired,

Various types of irregularity appear from spontaneous impulses arising not only from the sinus (tachycardia) but also from the auricle, a-v node and the ventricular terminations of the bundle (extra-systole). The auricular contractions are not always followed by ventricular, causing marked variations in the ventricular output and the blood pressure rapidly fluctuates. Auricular fibrillation appears and ultimately death takes place from ventricular fibrillation. This is the **THIRD STAGE**.



(Cushny)
 Fig. 51.—Digitalis on dog's heart. (A) normal tracing. (B) Small dose of digitalis causing therapeutic action : increased systole of both chambers and slight rise of blood pressure. (C) Toxic dose : marked slowing (partial heart block), irregular rhythm and lowered blood pressure. (D) Vagi cut : removal of slowing and high (toxic) blood pressure. (E) Final toxic stage : great irregularity of both the chambers with fall in blood pressure.

3. The bulk of the modern knowledge of the action of digitalis on *the human heart* has been obtained with the help of moving X-ray pictures and the electrocardiograph.

(i) With an adequate dose, digitalis reduces the size of a healthy heart and consequently lessens the output, may be 65 to 80% of the normal. The auriculo-ventricular conduction is lessened and the T-wave altered. During this period, the patient feels, that the heart is beating with greater force and he has some dyspnœa on exertion and cardiac pain (probably caused

by some interference with coronary circulation). But in a patient with circulatory failure, with diminished ventricular output, a sufficient dose of digitalis lessens the cardiac dilatation, restores the cardiac tone, increases the output and lessens venous stasis. The pulse rate if above normal is lessened. The action is mainly on the **heart muscles** including the auriculo-ventricular conducting mechanism.

(ii) **BLOOD VESSELS.**—The action on the **blood vessels** is less important. Smaller doses have no action but by perfusion experiment it has been found that digitoxin causes contraction of the splanchnic blood vessels, less so of the kidneys and even less of the limbs, brain and the coronary arteries. This is due to direct muscular action and is much feebler than the same on the heart muscle itself. The dose necessary for any vascular action in an intact animal is however high causing rapid death and is thus of no practical importance.

(iii) **BLOOD-PRESSURE.**—If the arterial blood pressure is previously low from atony of the heart muscles this is brought to normal but otherwise in spite of greater cardiac output, pressure is not appreciably raised as the veins are emptied more quickly and there is a freer passage of blood in the arterial system. This adjusted blood supply causes slight diminution of the tone of the vaso-motor centre. Diastolic pressure is consequently lowered increasing the pulse pressure.

In animal experiments in the second stage, the pressure may be lowered from diminished ventricular output and in the third stage, it is fluctuating from rapidly changing irregular cardiac action.

In a case of high blood pressure associated with circulatory stasis, digitalis is helpful and it even reduces the blood pressure. Here, on account of deficient circulation the vaso-motor system is in a state of overactivity to maintain the effective vascular pressure resulting in contraction of the peripheral arterioles. Administration of digitalis improves the general circulation by increasing the strength of cardiac contractions, the vaso-motor activity comes down almost to normal and the blood pressure especially the diastolic pressure falls.

(iv) **URINARY SYSTEM.**—Digitalis slightly increases the urinary output in a normal person involving the fluid portion and slightly chloride and uric acid. But if circulatory failure with oedema is present, the increase is much more, this being the channel of elimination of the extra fluid. The action is solely due to improved circulation through the kidneys.

(v) **ALIMENTARY SYSTEM.**—Digitoxin is absorbed from the stomach and the upper part of the small intestine fairly readily although other glycosides of this group as strophanthin are absorbed with difficulty and are largely destroyed in the alimentary tract. The effect on the gastric enzyme is not very much.

Digitalis increases the movements of the muscles of the stomach and intestine by its stimulating action on the vagal centre. So in some cases, there may be **nausea, vomiting** and **diarrhœa**. This action is especially marked when digitalis is continued beyond the therapeutic limit. It slightly increases the contraction of a gravid uterus and also of the bronchioles, spleen and other plain muscles.

(vi) MEDULLARY CENTRES.—In addition to its effects on the **cardiac centre**, it slightly increases the activity of the **respiratory centre** also, so that the breathing becomes deeper and quicker. Vomiting, that sometimes follows its prolonged administration, is partly central in origin. In toxic doses, convulsion is sometimes seen from cerebral stimulation.

(vii) ABSORPTION AND ELIMINATION.—Digitalis given orally especially as the tincture or as digitoxin or digoxin tablets, is fairly readily absorbed from the intestine. Local irritation on the stomach is prevented by taking the drug after food. The effect of a moderately high dose as 3 to 4 c.c. of the tincture is fairly rapid, a change in the T-wave being obtained in 3 to 4 hours and maintained for about 24 hours. Digitalis is partly oxidised in the system and partly excreted, the daily loss equalling about 0.12 g. of the dried leaf or 20 minims of tincture for an adult of moderate built. Digitalis is fixed in the heart muscle in a larger proportion probably by forming a combination with cholesterol (this is removable by repeated perfusion with Ringer's solution).

Strophanthin is more readily washed out and scillaren A even more readily : these consequently are less cumulative.

Digitalis is also found in the liver, kidneys and in the intestine : both the urine and the fæces thus help elimination. This being slow, even 20 days after administration some digitalis is yet present.

An œdematous patient on digitalis collects some digitalis in the body fluid. This may be mobilized on the administration of a mercurial diuretic and digitalis so collected in blood may even reach the toxic level.

It has been found that sixteen times the quantity of digitoxin are necessary to stop the heart of a living cat as of an isolated heart. Thus extra-cardiac tissues as skeletal muscles, liver and the kidneys take up a very much larger amount than the heart itself.

(viii) TOLERANCE.—No tolerance is established by its repeated administration.

The action on the decompensated human heart is thus somewhat of the *frog type*, more on the muscles than on the inhibitory mechanism.

THERAPEUTIC EFFECTS.—Digitalis is frequently given in many cases of cardiac dilatation with ventricular insufficiency, shown by dyspnœa on slight exertion or orthopnœa and general anasarca (**congestive** or mitral type of **heart failure**)⁴⁵². A fair number of such cases are associated with auricular fibrillation

also and readily improve but those that are not, show less striking improvement and this mainly depends on the condition of the heart muscles: larger the amount of functioning muscle fibres present, better is the response, extensive fatty or fibroid degeneration showing little results. Digitalis has a direct stimulating action on heart muscles in asthenic dilatation increasing the force of contraction. A more perfect and prolonged systole empties out the ventricles very effectively allowing more space for diastolic filling. Inhibitory action and diminished auriculo-ventricular conduction which may also operate, may help in lessening the heart rate which is high in most cases. All these combined allow the ventricles more time to fill up and when after a period of prolonged diastolic rest and better coronary filling, contract with a larger volume of blood, they do so more powerfully and the output into the arterial system is largely increased. In some of these cases, cardiac rate is not much lessened: yet the muscular tone and the force of contraction substantially improve. In any case, as circulatory velocity is also increased, more blood is abstracted from the distended veins: this reaches the ventricles and as a forcible systole puts the same into the arteries, the venous stasis is removed and the arterial circulation improves.

In these cases, the ventricles are already dilated and in a condition of hypotonus: these do not dilate any further during diastole, but become rather smaller with the recovery of the cardiac tone. When the stasis is removed, these tend to approach the normal size.

With this improvement, many of the symptoms of cardiac deficiency disappear. The patient becomes capable of more exertion without getting breathless, venous stasis in the kidneys is removed, and as more arterial bloods is freely circulating with an effective vascular pressure, the quantity of urine increases and this helps the removal of the dropsical fluid, which is usually present.

[Digitalis is often combined with theophylline (p. 532) and mercurial diuretics (p. 310) to have the full effect].

It will thus be evident that, in diseases of the heart, digitalis is indicated only when there is **venous stasis, ventricular atony and consequently mitral failure**. It is not of much use in functional or toxic disorders of the heart.

So the signs of improvement in a case of congestive heart failure are (i) relief of the symptoms of distress, (ii) recovery of cardiac tone and lessening of the cardiac area, (iii) increase

(452) R

Tinct. Digit. min. 15

Sp. Ammon. Aromat.

Tinct. Cardam. Co. aa min. 20

Aq. Chlorof. ad. fl. oz. 1

Every 3 to 4 hours for congestive heart failure.

of cardiac output as marked by adequate rise in arterial and fall in venous pressure, freer urination and lessening of body weight to reach the normal limit (caused by removal of dropsical fluid) and often (iv) slowing of the heart rate.

Given in **auricular fibrillation**, digitalis stops many of the auricular impulses from reaching the ventricles. The rate of the latter comes down almost to normal and in addition, the pulse becomes full and nearly regular. The systole becomes more efficient and the diastole more prolonged. The stasis in the ventricles as well as in the venous system, which is frequently present, is quickly removed, arterial circulation increases, venous pressure lessened and the general condition of the patient remarkably improves.

It is, however, necessary to continue digitalis in smaller doses for some time afterwards in order to maintain this control on the heart muscles and the A.V. bundle.

The cardiac irregularities of non-fibrillating cases also often disappear probably due to improvement of the cardiac nutrition.

It is given in **auricular flutter**. In addition to improving the cardiac tone, digitalis changes flutter to fibrillation and also lessens the conductivity of the bundle. On stopping digitalis, fibrillation disappears and the normal sinus rhythm is restored.

It is also of some value in supraventricular (nodal or auricular) type of **paroxysmal tachycardia** especially if quinidine has failed and congestive failure is imminent.

In many **early cases of heart disease** with myocardial deficiency which may ultimately lead to cardiac hypertrophy and dilatation and finally to congestive failure, administration of digitalis in small doses early even before signs of deficiency appear has been found useful.

In **aortic diseases**, digitalis is indicated only if venous stasis is present. In **right heart stasis** following chronic pulmonary diseases, digitalis is also useful: it increases the strength of the ventricular contraction and circulatory velocity which removes pulmonary congestion.

In **acute febrile conditions**, its action is still a matter of dispute. Recently it has been found that in many such conditions, the circulatory deficiency is due to vaso-motor failure myocardial weakness playing a subordinate part: digitalis consequently is not often indicated. Further the inhibitory mechanism being less sensitive in such cases and the myocardium also somewhat degenerated, signs of overaction are not apparent early enough. On continuous administration for sometime, serious symptoms of acute intoxication may develop even ending fatally.

It is slightly *antipyretic* in some febrile conditions but this is of no clinical value.

The mode of action may be either (a) increase of the activity of the temperature controlling centres (Harnack) or (b) depression of oxygen consumption and blood pressure following a temporary increase (Nylin).

THE METHOD OF ADMINISTRATION AND DOSAGE.—The following points should be remembered. (i) The glycoside, digitoxin is insoluble and rather unstable in water. Therefore digitalis should not be prescribed in mixtures but added to it immediately before administration. (ii) As the active principles deteriorate on storage, the tincture should not be of more than one year old from the date of manufacture : (iii) much better method is to administer the active substances in tablet form, either of the whole leaves or the glycosides made into tablets. (iv) The glycosides must accumulate in the heart muscles in certain quantity before it can produce its specific action, especially on the bundle. So the *route of administration* and the *quantity* are points of consideration.

Owing to the variable nature of its chemical constituents it is standardised biologically by observing its action on the heart of a frog or a cat, one frog or cat unit being that quantity which, when injected into the ventral lymph sac of a frog or intravenously, slowly and continuously in a cat, kills either animal of a definite body weight in a specified time. One *cat unit* is about one c.c. of the standardised tincture. It has been found that about 15 c.c. of the tincture must be administered to a man weighing about 150 lbs. who has not taken any digitalis within 10 days. to produce the therapeutic effect in 36 to 48 hours.

PREPARATIONS OF CHOICE.—(a) Of the *digitalis purpurea* products, usually the standardised tincture is prescribed, but now the tablets are more frequently used.

(i) *Digitalis leaf* as tablets available in 0.1 g. tablet *digifortis* and tablet *digitalis*, has a popularity and is easily administered. (ii) Recently crystallised *digitoxin* (*digitoxin tablets* 0.1 mg. and 0.2 mg. or *crysto-digin* 0.1 mg. tablets) available and is gaining popularity. *Digitalin-Nativele* is a digitoxin preparation. The absorption from oral administration is quite rapid and side effects are not much.

(b) Of the *digitalis lanata* products, digoxin has been found quite useful. Administered in 0.25 mg. tablet 3 to 6 times daily (depending on the severity of decompensation), it has more rapid action.

Digoxin is available as 0.25 mg. tablets and vials of 10 c.c. and 30 c.c., 0.5 mg. per c.c. and 0.5 mg. ampoules. *Digilanid* as tablet, (0.25 mg.), liquid (1 ml. has 0.5 mg.) and ampoules (0.2 mg. in 1 ml.). These have all the 3 glycosides. The glycoside C available as *Cedilanid* is claimed to have a wider margin of therapeutic efficiency : used in congestive heart failure with or without abnormal rhythm, tablets (0.25 mg.), solution (1 mg. in 1 ml.) and ampoule (0.2 mg. in 1 ml.) are used.

APPROXIMATE THERAPEUTIC EQUIVALENTS

| Preparations | Tincture Equivalent |
|---|---------------------|
| <i>Leaf</i> 0.1 g. | 10 min. |
| <i>Digitalin</i> Nativelle 0.1 mg. | 12 min. |
| <i>Digitalin</i> Nativelle or <i>Digitoxin</i> 0.25 mg. | 30 min. |
| <i>Digoxin</i> , <i>Digilanid</i> 0.25 mg. | 15 min. |
| <i>Lanatoside C</i> 0.25 mg | 15 min. |

DOSE.—Digitalis preparations are mainly used for conditions with ventricular dilatation and congestive failure. Most of the cases of chronic auricular fibrillation are associated with congestive failure.

The doses and the frequency of administration are based on the urgency of symptoms.

(1) In **chronic myocardial insufficiency** (i) *before the symptoms* have appeared, one 0.1 g. of the leaf tablet daily : (ii) *with moderate symptoms*, 0.1 g. leaf tablet 3 times daily for a week and 0.1 g. once daily afterwards (maintenance dose) ; (iii) *more marked symptoms*, requiring rapid digitalisation, digoxin 1.5 mg., digitoxin 0.6 mg. or leaf tablet 0.6 g. (six tablets) daily is advised : (iv) *for urgent cases*, digoxin 2.5 mg., digitoxin 1 mg. or leaf 1 g. (10 tablets) is the initial dose : repeated 6 to 8 hours after, 4 tablets, 3 tablets, 2 tablets and if the full digitalis effect is produced, one tablet daily. The signs of overaction or underaction are to be carefully watched for and the dose is regulated (increased or diminished) accordingly.

(2) In **acute myocardial insufficiency** or when the symptoms are very urgent, if no digitalis preparations were given within 10 days, ouabain 0.25 mg., strophanthosid 0.2 mg., lanatoside C 0.8 mg., digoxin 0.5 mg. or digitoxin 0.6 to 1 mg. in glucose solution is given very slowly intravenously. The effects are maintained by subsequent oral administration.

(3) **Chronic auricular fibrillation** with symptoms of circulatory failure may have the above dose scheme according to urgency. When relieved, quinidine therapy (p. 345) is to be considered.

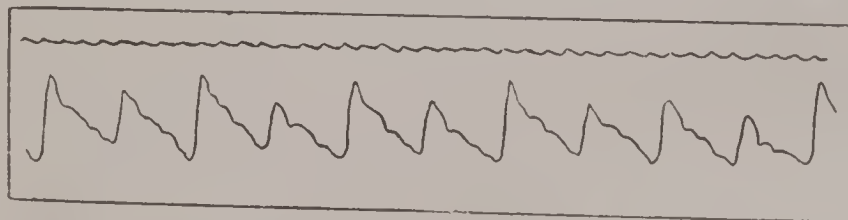
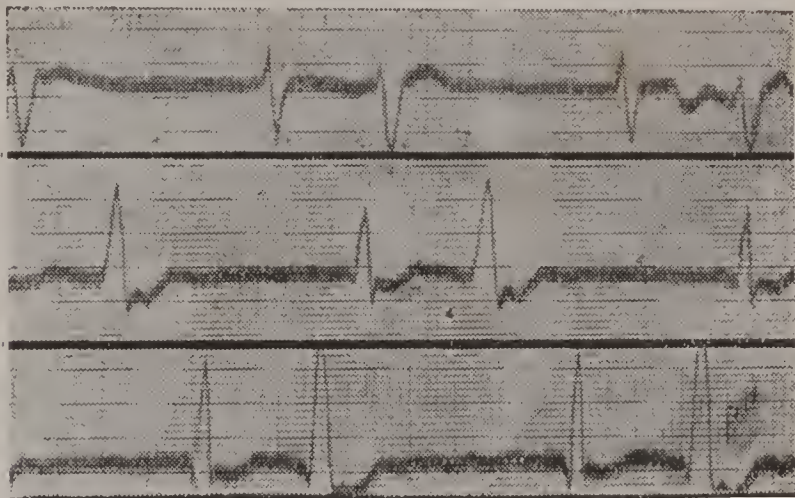


Fig. 52.—Pulsus alternans (a normal beat is followed by a smaller beat) as a result of overaction of digitalis. (After Mackenzie)

(4) In **auricular flutter** 0.6 mg. digitoxin initially, 2 or 3 doses of 0.4 mg. four hourly and daily dose of 0.2 mg. may either restore the normal rhythm or bring in auricular fibrillation when further administration is stopped : or 1.2 mg. initially and after 8 hours, 0.2 mg. and repeated every 6 hours till the normal rhythm is established.

[In all cases of congestive failure, careful regulation of rest and exertion, of diet, fluid and sodium intake : also regulation of the bowels without drastic purgation and diuretics (mercurials and theophylline) are auxillary items].

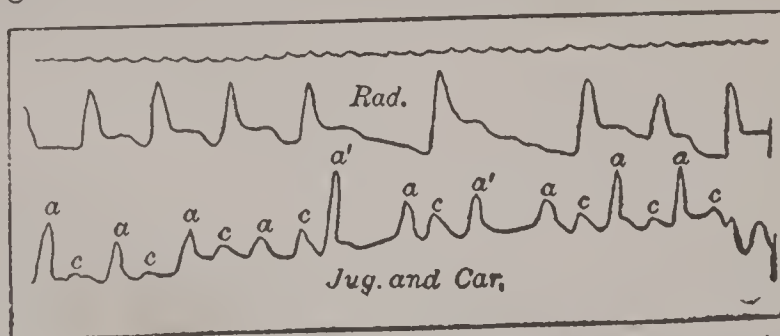
Too small a dose of digitalis is useless. Once the effect is produced, only a maintenance dose is necessary just to make up for the daily loss. This is about 20 minims of tincture or one tablet of any of the solid preparations. Elimination by the



(Original)

Fig. 53.—Overaction of Digitalis in a case of mitral stenosis causing pulsus alternans.

Kidneys is rather fitful. Toxic symptoms may therefore develop suddenly (**cumulative action**) and so a careful watch should be kept to see when the specific action is produced and stop it as soon as the signs of supersaturation appear. These are the following :



(After Mackenzie)

Fig. 54.—Overaction of digitalis : occasional dropped auricular beat (a' is not responded to by the ventricle).

(i) Appearance of *extra systole* (excessive myocardial irritability) or *undue slowing* (inhibitory action causing whole heart slowing or dropped beat) of the pulse as 50 or less per minute, sometimes *pulsus alternans*.

Heart block may be auriculo-ventricular and less commonly sino-auricular: this is more often from inhibitory mechanism (abolished by atropine) and rarely from direct action on the junctional tissues (diseased human heart behaving like a frog's heart).

(ii) *Headache, nausea, vomiting* and more rarely *diarrhœa*.

(iii) The electrocardiographic observation shows inversion of T-waves and various types of arrhythmia afterwards increased auriculo-ventricular interval: less commonly auriculo-ventricular, and rarely sino-auricular block (dropped beat and pulsus alternans).

Digitalis should at once be stopped: the extra quantity above the therapeutic limit is eliminated and all troubles disappear in a few days.

ACUTE DIGITALIS POISONING.—One single very big dose may not cause any symptoms or there may be nausea, vomiting, colic and diarrhœa. Precordial pain, general depression, headache, giddiness, severe prostration and collapse may follow.

CONTRA-INDICATIONS.—Calcium should not be given intravenously to a digitalized person and a combination of ephedrine and digitalis is more toxic than either of these alone. Digitalis should not be given in partial heart block for the risk of inducing complete block.

In constricting pericarditis and in ventricular tachycardia digitalis is contraindicated.

With the above precautions, in many cases of chronic heart disease, it may be necessary to continue digitalis in maintenance dose for months and even for years fairly safely.

SUMMARY.—Digitalis increases the force of contraction especially of the atonic and badly nourished heart muscles directly and to a less extent through the inhibitory mechanism. It partly blocks the bundle, prolongs the diastole and improves the force of systole of the ventricles. The cardiac output increases, ventricular rate comes down and œdema, if any present, disappears. The force of auricular contraction and its tone also improves. It is indicated in all conditions of cardiac decompensation with a tendency to venous stasis and especially if auricular fibrillation is also present. The method of administration and the dose depend on the urgency of symptoms. But doses above the therapeutic limit increase the irritability of the heart muscles and give rise to irregularities of the rhythm also gastro-intestinal disturbance. It is not indicated in compensated heart disease and also in acute febrile conditions.

Non-official Preparations

NATIVELE'S DIGITALINE granule (gr. 1/240 or 0.25 mg. white and gr. 1/600 or 0.1 mg. pink) contains mainly digitoxin (first isolated by Nativelle in 1859) and is an effective preparation.

DIGALEN (said to be isomer of digitoxin) available as tablet, oral solution or ampoule: 1 c.c. = 0.3 mg. of glycoside.

Dose, 10 to 15 minims or more.

DIGIPURATUM.—Purified extract of all the active glycosides.

Dose, $\frac{1}{2}$ to 2 grains.

DIGIFORTIS and DIGISTAN liquid are $1\frac{1}{2}$ times as strong as the tincture of digitalis. These are dependable digitalis preparations.

STROPHANTHUS (*Strophanth.*), *Strophanthi semina*

Strophanthus consists of the dried ripe seeds of *Strophanthus kombe* freed from awns. The principal active constituent is *Strophanthin*.

The seeds are obtained from the equatorial region of West Africa. Lanceolate, pointed towards the apex, narrowed but obtuse at the base : flattened and with a ridge running from the centre to the apex. Covered with longitudinal rows of silky appressed hairs directed towards the apex, greyish green to greyish fawn coloured. Size about $\frac{1}{2}$ " \times $\frac{1}{8}$ " (12 to 18 mm. \times 3 to 5 mm.).

STROPHANTHI PULVIS (*Strophanth. Pulv.*), greyish yellow powder with brown specks.

Tinctura *Strophanthi* (*Tinct. Strophanth.*), See p. 60.

DOSE, 2 to 5 minimi or 0.12 to 0.3 ml., standardised biologically. This also, like digitalis, is administered along with water immediately before use, instead of being dispensed in a mixture.

OUABIANUM (*Ouabian.*), G-Strophanthin, $C_{29}H_{44}O_{12} \cdot 8H_2O$.

This is a crystalline glycoside, obtained from the seeds of *Strophanthus Gratus* or from the wood of *Acokanthera Schimperi*.

Small colourless crystals or white crystalline powder : inodorous and bitter : soluble in 100 parts of water and in dehydrated alcohol : almost insoluble in solvent ether and chloroform.

DOSE, 1/500 to 1/240 grain or 0.12 to 0.25 mg. intravenously.

Injectio *Ouabaini* (*Inj. Ouabain.*), See p. 45.

DOSE as of Ouabain. When no dose is stated, a solution containing 0.25 mg. in 1 ml. (about 1/240 gr. in 15 min.) shall be dispensed.

Pharmacology [and Therapeutics]

Strophanthus acts on the heart muscles, similarly to digitalis, but little on the blood vessels, medulla and even less so on the stomach, the intestine and other unstriated muscle fibres. The glycoside is easily destroyed by the digestive ferments and as a result, when given by the mouth it is less effective than digitalis. *Strophanthin* given parenterally is eliminated quickly so much so that it entirely disappears from the system in 5 days and hence it is **not much cumulative**. The action consequently is **more shortstaying** and **less sustained** than that of digitalis. Being soluble in water, the best method of administration is to give the glycoside ouabain or *strophanthin* intravenously, 1/240 (0.25 mg.) to 1/120 grain, (0.5 mg.) which shows its action in less than two hours (often earlier) and as it is short staying, the effect is maintained by giving digitalis orally. Ouabain is about twice as potent as *strophanthin-K* and has now more or less replaced *strophanthin*. If the patient is already taking digitalis for some time, *strophanthin* should not be given intravenously as the combined effect of the two may cause dangerous heart block. Further the injection should not be repeated in 24 hours.

Strophanthin is available in 0.3 to 0.6 mg. tablets and ouabain in 0.25 or 0.5 mg. per c.c. ampoules. *Strophosid*, k-strophanthoside is available in 0.25 or 0.5 mg. per c.c. ampoules.

Further in some people especially in a weak patient, strophanthin may cause sudden unconsciousness and should be injected slowly well diluted with isotonic glucose solution.

Being less vasoconstricting, it is expected to be a better diuretic than digitalis, but clinically it is hardly ever found to be so.

Strophanthus is sometimes given by the mouth also in the beginning, and is followed by digitalis, for its prompter action and sometimes digitalis and strophanthus are alternated⁴⁵². But its therapeutic effect from oral administration is uncertain and is now seldom used in that way.

SUMMARY.—*Strophanthus K* as tincture of straphanthus orally and *Strophanthus G* as ouabain intravenously are used for quick digitalis action. Ouabain is more commonly used for an emergency (p. 655) and is dependable. Strophanthin may also be used intramuscularly or intravenously but less certain. The action produced is maintained by digitalis preparations orally.

INDIAN STROPHANTHUS (Not official).—Several species are indigenous to India and the Malayan Peninsula. But their glycoside contents are still unknown.

SCILLA (*Scill.*), Squill

Squill is the bulb of *Urginea Maritima* whose outer scales have been removed and then cut into slices and dried, also called *white squill*. These are pale yellow, slightly translucent strips, tapering at both ends, sometimes adhering, about $\frac{1}{2}$ to 2 inches (0.5 to 5 cm.) long: inodorous but has a bitter mucilaginous and acrid taste. Should be kept in a desiccated atmosphere.

It is obtained mainly from the Mediterranean Coasts.

SCILLÆ PULVIS (*Scill. Pulv.*), white powdered squill.

The chief active constituents are two glycosides, *Scillaren A* (crystalline) and *Scillaren B* (amorphous) often collectively called *Scillaren*.

Dose, 1 to 3 grains or 60 to 200 mg.

URGINEA (*Urgin.*), Indian Squill, Not Official

The Indian variety, *Urginea Indica* grows in the sea-coast areas of the Deccan and Chittagong and is prepared and stocked in the above way. The appearance is the same as of the above.

Dose, 1 to 3 grains or 60 to 200 mg.

OFFICIAL PREPARATIONS.—(i) **Acetum Scillæ**, Vinegar of squill: See p. 36. Dose, 10 to 30 minims or 0.6 to 2 ml. (ii) **Oxymel Scillæ** (*Oxymel. Scill.*), See p. 51. Contains 5% w/v of squill. Dose, 30 to 60 minims or 2 to 4 ml. (iii) **Syrupus Scillæ** (*Syr. Scill.*), See p. 53. Contains 1.5% w/v of squill. (All these three are acid in reaction). Dose, 30 to 60 minims or 2 to 4 ml. (iv) **Tinctura Scillæ** (*Tinct. Scill.*), See p. 60. (10%). Dose, 5 to 30 minims or 0.3 to 2 ml. For all these, the Indian squill may also be used.

(452) B

Tinct. Strophanth, min. 5

Tinct. Nuc. Vom. min. 15

Tinct. Cardam. Co. min. 3)

Aq. Chlorof. ad. fl. oz. 1

A cardiac tonic.

Pharmacology [and Therapeutics]

Squill also contains active glycosides having action resembling digitalis. It has been found by perfusing a mammalian heart that squill is **more powerful than digitalis** but less than strophanthus; it probably causes a higher rise of **blood pressure** also. But given by the mouth, squill is absorbed much less rapidly and completely than either digitalis or strophanthus. Intravenous administration of a stable preparation of it is likely to be effective but is not yet readily available nor is sufficiently popular. So it is not suitable for use in heart diseases.

Squill is **irritant** to all forms of plain muscles, especially to the stomach and intestine much more than digitalis. In large doses, it causes nausea and vomiting but if given in small doses, it increases the **bronchial secretion**^{453, 455} mainly by a reflex action through the stomach, irritating the vagal terminals in it and to less extent, by acting directly on the bronchial glands in the process of its excretion. [It is frequently used in cough mixtures in subacute or chronic bronchitis also cough of congestive heart failure].

It is a more powerful **diuretic**⁴⁵⁶ than other drugs of the digitalis group and probably acts by directly irritating the renal cells during excretion. It is prescribed in pill form with digitalis leaves for cardiac dropsy (see p. 310)]. It should not be given in acute nephritis. The Indian squill, *urinea*, has the same action and is an effective substitute.

SUMMARY.—The glucosides orally have feeble digitalis action but more commonly used as an **expectorant** (pulmonary reflex from the gastrointestinal tract) and **diuretic** especially in cardiac dropsy.

Non-official Preparations

ANASARCIN in tablet contains the active glycosides of squill and is used for cardiac dropsy.

SCILLAREN (this has both the glycosides), in 0.8 mg. tablets or in solution of 0.8 mg. per c.c., 3 to 4 doses orally or in ampoule of 0.5 mg intravenously, is given in cardiac dropsy.

URGININ for oral use in 0.5 mg. tablets and 1 mg. intravenously, is given in cardiac dropsy.

(453) \mathcal{R}
Tinct. Ipecac. min. 10
Oxymel Scill. min. 60
Tinct. Tolu. min. 30
Aq. Camph. ad. fl. oz. 1
Mix. For chronic bronchitis.

(454) \mathcal{R}
Pot. Acet. gr. 15
Syr. Scill. min. 30
Tinct. Ipecac. min. 8
Aq. Menth. Pip. ad. fl. oz. 1
Mix. For subacute bronchitis.

(455) \mathcal{R} *Gee's Linctus.*
Tinct. Opii Camph.
Oxymel Scill. aa. min. 120
Syr. Tolu. ad. fl. oz. 1
One tea-spoonful for irritable cough.

(456) \mathcal{R}
Tinct. Scill. min. 10
Sp. Juniper. min. 8
Sp. Æther. Nitros. min. 20
Syr. Aurant. min. 60
Inf. Buchu. Rec. ad. fl. oz. 1
For chronic nephritis.

APOCYNUM CANNABINUM.—The tincture, in 5 to 20 minims doses, is used in many dropsical conditions⁴⁵⁷ and acts as a powerful diuretic. But it is a gastro-intestinal irritant and should be given well-diluted with water.

TERMINALIA ARJUNA.—This has some reputation in Ayurveda as a heart tonic. But its active principles have not been as yet isolated in a stable form. Some species of it are therapeutically active⁴⁵⁸. (Caius, Mhaskur and Issac)

CACTUS.—Believed to have some tonic action on the heart but not proved. Cactina pellets are used for palpitation due to functional causes.

ACONITUM (*Aconit.*), *Aconiti Radix*, Aconite root, *Bisha*, *Mithabish*

This is the dried root of *Aconitum Napellus*, dark brown in colour, obconical, shrivelled usually 4 to 10 cm. × 1 to 3 cm. wide at the crown to which is attached the base of the aerial stem or the remains of a bud with many thin rootlets or root scars and has a central axis with rays inside in light grey or dark brown in colour.

Available in India from Sikkim, Bhutan, Darjeeling and Kashmere.

ACONITI PULVIS (*Aconit. Pulv.*) is greyish brown in colour.

It contains 0.5% of the active principle, an alkaloid, *aconitine*. It has two other alkaloids, *aconine* and *benzaconine*.

OFFICIAL PREPARATION.—**Linimentum Aconiti** (*Lin. Aconit.*), See p. 48.

TINCTURA ACONITI (Not official).—Powdered root 1, alcohol (70%) to contain 0.04% of the alkaloids.

Dose, 2 to 5 minims or 0.12 to 0.3 ml.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, aconite has little action on the intact skin. But, rubbed in with an alcohol, chloroform or fat it causes **tingling sensation** followed by local **anaesthesia**. It is therefore sometimes added to liniments, but is not always safe, as a toxic amount of the alkaloid may be absorbed especially when it is rubbed in. It is mostly used as *paint* in superficial painful conditions and neuralgias^{459, 460}.

The motor nerve fibres are also similarly affected although to a less extent. At first these are stimulated causing involuntary twitchings and later on, paralysed and muscular power is lost.

(457) R
Pot. Acet. gr. 15
Tinct. Apocynum. min. 10
Ext. Punarnava Liq. min. 30
Syr. Aurant. min. 60
Inf. Buchu Rec. ad. fl. oz. 1
For general anasarca.

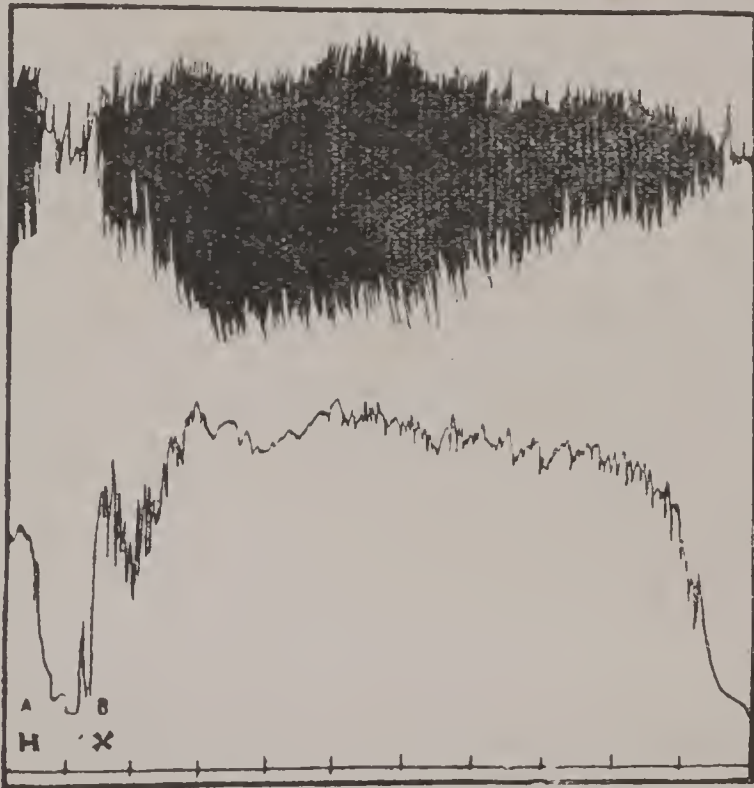
(458) R
Pot. Acet. gr. 20
Diuretin gr. 5
Ext. Arjun. Liq. min. 60
Inf. Scopar. ad. fl. oz. 1
For cardiac anasarca.

(459) R
Menthol. gr. 5
Lin. Aconit.
Lin. Bellad. aa. min. 240
(Lucas)
To paint over a painful part,

(460) R
Menthol. gr. 2
Tinct. Aconit. min. 60
Tinct. Myrrh.
Liq. Iod. Mit.
Glycer. aa. min. 140
Paint for painful gum.

TAKEN INTERNALLY ORALLY, the alkaloid is quickly absorbed and produces its specific action.

On the mouth and the throat, it gives a hot burning sensation, pricking and roughness, resulting in salivation, vomiting and tickling with itching in the nose. After a short time, the action is reversed, there being paralysis of the nerve-endings. The sensory feeling in general including the sense of taste is weakened.



(After Dixon)

Fig. 55.—At A aconite is injected intravenously ; vagal stimulation causes stoppage of heart (upper curve) and fall in blood pressure (lower curve). At B, the vagi are cut. Heart beat becomes forcible and rapid afterwards weak and fibrillating. Blood pressure is at first slightly raised and then falls and death follows from fibrillation.

CIRCULATION.—A *small dose* as 2 to 8 minims of the tincture has little effect on the circulation except slight slowing. [It is sometimes prescribed in cardiac neurosis⁴⁶¹]. A *bigger dose* causes nausea and vomiting which **accelerates the heart rate** : By action on the vagal centre, the heart rate is soon slowed, the contraction is enfeebled, the cardiac output is lessened and the blood pressure falls. A *still larger dose* sometimes acts directly

(461) R
Sod. Brom. gr. 10
Tinct. Aconit. min. 3
Inf. Gent. Co. Rec. ad. fl. oz. 1
For palpitation neurosis.

on the **heart muscle**. The rate is suddenly accelerated, excitability increased, conduction impaired and contractility also altered. Extra-systole, disturbed auriculo-ventricular rhythm and pulsus alternans appear. There is considerable fluctuation in the blood pressure which falls below normal. Finally, death follows from ventricular fibrillation.

MEDULLA.—At first there is some stimulation followed by depression especially of the respiratory and vaso-motor centres. In small doses, the respiration is increased in depth and frequency, but with a bigger dose it becomes slower, laboured and sometimes there is marked dyspnoea.

Owing to the depression of the vaso-motor centre, there is increased loss of heat from the skin, and so the **temperature falls**⁴⁶² especially in fever. [It was formerly used in short catarrhal fevers but owing to its toxic action, it is now-a-days seldom used. Its action as antipyretic is also not very certain and better antipyretics are available. It is especially contraindicated in acute febrile conditions that are likely to persist, as pneumonia or typhoid fever].

Aconite, mitigated (probably also chemically altered by soaking in cow's urine and exposing to sun's rays for 3 to 4 days (*Sodhana*), is used in Ayurveda as antipyretic : said to be cardiac tonic and not depressant.

Dose, $\frac{1}{4}$ to $\frac{1}{2}$ grain in pill.

RESPIRATION.—Given in a toxic dose, aconitine affects respiration early : the rate is slowed and movements diminished causing asphyxia.

SUMMARY.—Aconite is so poisonous that it is now-a-days seldom used in medicine. It acts mainly on the sensory nerve-endings as *pain-tiniment*, initial stimulation being followed by their paralysis causes analgesia.

VERATRINE (Not official), an alkaloid obtained from various species of *Veratrum*, resembles aconitine in first stimulating and then depressing both sensory and motor nerve-endings. In addition, it prolongs the period of muscular contraction and diminishes the relaxation of both the skeletal and cardiac muscles. The heart finally stops in systole.

It is sometimes prescribed to reduce the raised blood pressure. *Veratrine*, 1 c.c. hypodermically is given in eclampsia : repeated as necessary in half dose. *Protoveratrine*, 1.4 mg./kg. bodyweight intravenously is coming into use for hypertension.

NITRITES

1. **SPIRITUS ÆTHERIS NITROSI** (*Sp. Æther. Nitros.*), Sweet spirit of Nitre.

PREPARATION.—Nitric acid 15, sulphuric acid 10, copper 10 and alcohol (90%) 100 are mixed and then distilled, the distillate being received in 90% alcohol. The distillate contains ethyl nitrite, $C_2H_5O_2N$, (1.25 to 2.5%), alcohols and the oxidation products,—aldehyde, paraldehyde, acetic acid and acetic ether.

(462) R

Salicin. gr. 5

Tinct. Aconit. min. 2

Aq. Camph. ad. fl. oz. 1 (Lucas)

In the beginning of coryza.

A transparent, yellowish liquid with characteristic odour and taste.

It should not be acid in reaction. It must be stocked in dark sealed bottles. Its impurity is an *excess of acetic acid*.

DOSE, 15 to 60 minims or 1 to 4 ml.

INCOMPATIBLES.—Iodides, bromides, iron sulphate, antipyrin, salicylates and tannic acid.

LIQUOR ETHYL NITRITIS (Not official) —Contains $2\frac{1}{2}$ to 3% of ethyl nitrite in 25 of dehydrated alcohol and 5 of glycerin.

A clear and transparent fluid with a characteristic apple-like smell.

DOSE, 15 to 60 minims or 1 to 4 ml.

2. AMYLIS NITRIS (*Amyl. Nitris*), Amyl Nitrite.

Amyl nitrite is chiefly nitrites of *iso*-butyl carbinol $(\text{CH}_3)_2\text{CH}.\text{CH}_2.\text{CH}_2.\text{OH}$, and *sec*-butyl carbinol $(\text{C}_2\text{H}_5)(\text{CH}_3)\text{CH}.\text{CH}_2.\text{OH}$ with other nitrites of the same series. Prepared by the esterification with nitrous acid of the fraction of fusel oil which distils between 128° and 132°C . It must have 90% of the nitrites, calculated as $\text{C}_5\text{H}_{11}\text{O}_2\text{N}$.

A clear yellow liquid, with a characteristic smell and pungent aromatic taste : insoluble in water but soluble in alcohol (90%) and in solvent ether. Should be kept in a well-closed container, protected from light and stored in a cool place.

DOSE, 2 to 5 minims or 0.12 to 0.3 ml. By inhalation.

3. NITROGLYCERIN, Trinitroglycerin, Trinitrin, Glonoin oil. Nobel's blasting oil. (Not official).

It is highly explosive and is not used but one of its preparations is official and of therapeutic value.

TABELLÆ GLYCERYLIS TRINITRATIS (*Tab. Glyc. Trinit.*), Trinitrin tablet.—Nitroglycerin 1/130 grain, 0.5 milligram, with a chocolate basis 0.3 gm. to avoid explosion. Each tablet if not otherwise stated, should contain 1/130 gr.

DOSE, 1/130 to 1/60 grain or 0.5 to 1 mg.

4. SODII NITRIS (*Sod. Nitris.*), NaNO_2 .

Prepared by reducing sodium nitrate with metallic lead. Contains not less 95% of NaNO_2 . Colourless or slightly yellow crystalline or granular powder, freely soluble in water.

DOSE, $\frac{1}{2}$ to 2 grains or 30 to 120 mg.

TABELLÆ ERYTHRITYLIS TETRANITRATIS (*Tab. Erythrityl. Tetranit.*) Not official.—Prepared by moist granulation, using as moistening agents an ethereal solution of stearic acid and alcohol (45%), drying without using heat and compression. Each if not otherwise stated should contain $\frac{1}{2}$ gr. of diluted erythrityl tetranitrate.

DOSE, $\frac{1}{2}$ to 2 grains or 30 to 120 mg.

Pharmacology [and Therapeutics]

Chemically a nitrite is $\text{O}.\text{NO}$, which is attached to a metal or alkyl through an oxygen atom. A nitrate is $\text{O}.\text{NO}_2$ which breaks to acts as a nitrite. Thus nitroglycerin (trinitrate of glycerin) is $\text{CH}_2 (\text{ONO}_2).\text{CH} (\text{ONO}_2) \text{CH}_2 (\text{ONO}_2)$: this is broken down into nitrites and nitrates and its action is wholly from nitrites formed.

The important systemic actions of the drugs of the Nitrite group are as follows :

- (i) Paralysis of **plain muscles** especially of the arterioles.
- (ii) In toxic doses, change of **hæmoglobin** to methæmoglobin and nitric-oxide-hæmoglobin.

CIRCULATION.—The nitrite effects are most apparent and quick after inhalation of a few drops of amyl nitrite. There is generalised **vaso-dilatation** and **fall in the blood pressure**, due to the paralysis of the *muscular coat* in the walls in the blood vessels by *direct action*; best shown on the blood vessels of the skin of head and neck (causing flushing of the face, throbbing of the carotids, a sensation of heat and headache) and of the splanchnic area. The arterioles are more affected than the veins, and the blood collects in the splanchnic area. Coronary and retinal blood vessels are also dilated but not the pulmonary.

These are *not due* to (a) affect on the *vasomotor centre* as perfusion of the medulla with a solution of the drug has no vaso-dilator affect and (b) *not on* the peripheral *nerve endings* as stimulation of the splanchnic nerves (vaso-constrictor) causes some rise of blood pressure: (c) perfusion into the artery of an amputated limb of an animal causes vaso-dilatation.

The blood pressure at first slightly rises partly for the medullary stimulation by the pungent vapours of amyl nitrite inhaled and also partly for the increased cardiac output caused by the quickening of the heart. But as the blood vessels are soon much dilated, especially of the splanchnic area, the pressure quickly falls. This fall in blood pressure is not however as marked or as constant in a human being as in an anæsthetised animal.

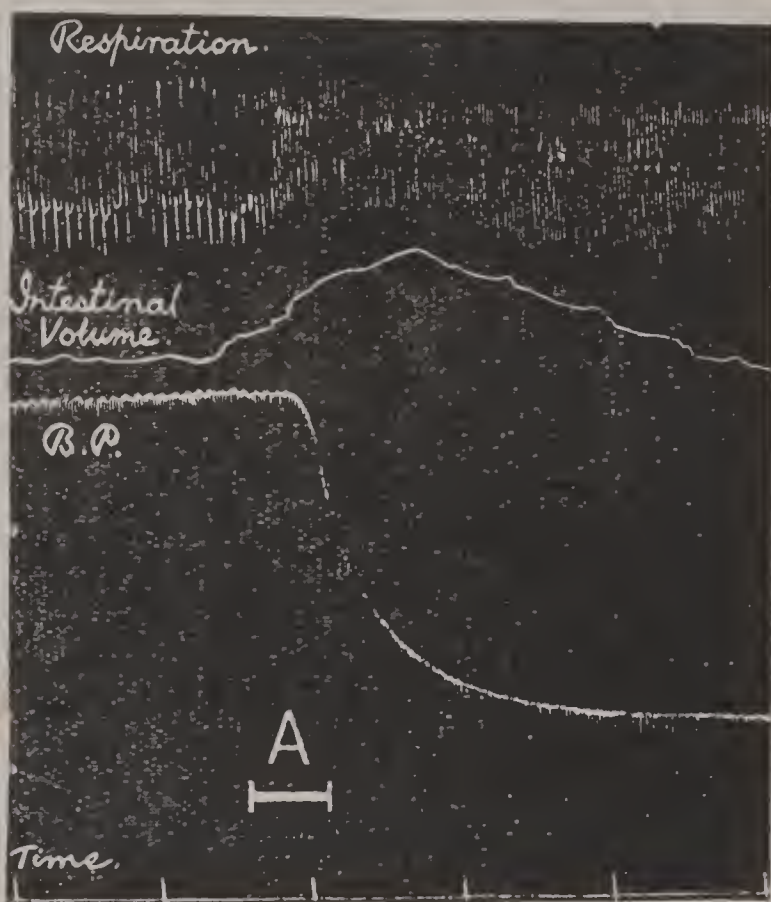
The **heart beats faster** because (a) less blood is circulating in the medullary centres, the cardiac inhibitory centre is depressed and (b) probably the acceleratory centre is excited. This is a *carotid sinus reflex*. More rapidly the pressure is lowered, greater is the quickening. This tends to lessen the output of the heart per beat. Although there is very little direct action on the heart muscle, a moderate dose improves the coronary circulation and lessens the peripheral resistance which sometimes helps the weak heart struggling against high blood pressure; but large doses lessen the coronary circulation and paralyse the heart muscles: the circulation becomes slow and weak.

OTHER PLAIN MUSCLES as those of the intestine, biliary passages, ureter and bronchioles are also moderately relaxed. [The nitrites are sometimes useful in **colicky conditions**, intestinal, biliary or renal (See p. 529) and also in **bronchial asthma**].

RESPIRATION.—Amyl nitrite given by inhalation, at first arrests the respiration from reflex action but soon makes it deeper and more rapid probably due to the fall of blood supply to the respiratory centre in the medulla. If, however, the administration is continued long, breathing becomes slow and shallow and death takes place from asphyxia.

NERVOUS SYSTEM.—There is no marked action on the nervous system. Only the *medulla* is slightly affected: at first reflexly

when amyl nitrite is inhaled and afterwards by the fall of blood pressure. The cardio-acceleratory and respiratory centres are stimulated and cardio-inhibitory one depressed.



(After Dixon)

Fig. 56.—Effect of amyl nitrite on *respiration* (this is quickened), *intestinal volume* (this is increased from dilatation of splanchnic blood vessels) and *blood pressure* (this is lowered).

The throbbing in the head, a sense confusion and headache are due to vaso-dilatation and lowered cerebral circulation.

Given in big doses, there is a feeling of giddiness and weakness passing on to stupor. There may be disturbance of colour vision (a black spot on a white background appears to have a yellow followed by blue ring) and convulsive movements which are cerebral in origin, probably due to formation of methæmoglobin and lowered cerebral circulation.

Blood.—Only in toxic doses. hæmoglobin is changed into methæmoglobin and nitric oxide hæmoglobin. The blood assumes chocolate colour and its oxygen-carrying power is lowered. This is more marked in lower animals than in a human being. In such doses, these are gastro-intestinal irritants also, causing vomiting and diarrhœa.

Temperature.—This is slightly lowered, especially when raised in fever, on account of increased radiation of heat from the skin caused by vaso-dilatation and sweating.

Kidneys.—There is **not much change** in the urinary flow. The effect of dilatation of the renal vessels is counteracted by the fall in blood pressure. Nitrites are partly changed into nitrates, eliminated by kidneys and partly destroyed in the system. Amyl nitrite is completely oxidised and almost entirely disappears. With a small dose, the blood pressure is not much lowered and urinary secretion may be slightly increased. But a big dose may so lessen the renal circulation that there may be even anuria.

1. SPIRITUS ÆTHERIS NITROSI.—Its two powerful ingredients, namely ethyl nitrite and acetic ether, are responsible for its therapeutic properties. Its action, therefore, is not exactly like other nitrites.

Applied Externally, owing to its having a little ether in it, it acts as a **rubefacient** and mild local **anæsthetic** but is not used as such.

Taken Internally, is a **reflex stimulant**⁴⁶³ to the heart and respiration and is a **stomachic** and **carminative**. It is a **diaphoretic** and feebly **antipyretic**⁴⁶⁴.

[It is one of the common ingredients of a “fever mixture” and is sometimes given in short fevers associated with respiratory catarrh].

From its general action as nitrite, it acts as a **vaso-dilator** of the peripheral blood vessels of the skin as well as of the kidneys. Its action as a diaphoretic is intensified by keeping the skin warm with proper coverings.

If the skin is not specially kept warm, vaso-dilating action is more marked on the kidneys, resulting in **diuresis** [and is useful in general anasarca of nephritis with scanty secretion of urine⁴⁶⁵].

2. AMYL NITRITE.—Its speciality is its rapid action. It is available in glass pearls containing 3 to 5 drops. One such crushed and inhaled, immediately shows the typical nitrite action. It is of no use orally as is partly destroyed in the gastro-intestinal tract. An old sample may be decomposed and not to be used.

Throbbing of the head, flushing of the face and **lowering of blood pressure** are apparent. The respiration after momentary stoppage becomes quicker and deeper. The effects are of short duration, disappearing in a few minutes. Continued inhalation

(463) B

Sp. Æther. Nitros.

Sp. Ammon. Aromat.

Sp. Chlorof. aa. min. 30

Aq. Camph. ad. fl. oz. 1

A diffusible stimulant.

(464) B

Sp. Æther. Nitros.

Tinct. Opii Camph. aa. min. 30

Liq. Ammon. Acet. Dil. min. 60

Aq. Anis. fl. oz. 1 (Lucas)

A diaphoretic-antipyretic.

(465) B

Pot. Acet. gr. 20

Sp. Æther. Nitros. min. 30

Liq. Ammon. Acet. Dil.

min. 30

Syr. Aurant. min. 60

Inf. Buchu Rec. ad. fl. oz. 1

A diuretic for subacute nephritis.

may lead to headache, dizziness, intoxication, temporary loss of consciousness and even convulsions. The pupils are dilated. The pulse become slow and respiration yet quick but irregular. The effects however, pass off in about 10 minutes.

If animals are made to inhale a large quantity of amyl nitrite, on account of the formation of **methæmoglobin**, the blood can no longer act as oxygen carrier and so they get cyanosed and finally die of asphyxia.

Amyl nitrite absorbed in the blood probably forms nitrites of alkalies, these undergo partial oxidation and appear in the urine as nitrates and nitrites and a fraction probably undergoes further changes.

3. **NITROGLYCERIN**.—It is really a nitrate and absorbed unchanged ; it is reduced in the blood into nitrite and acts more **slowly** but **powerfully** than amyl nitrite and its action is more **prolonged**, lasting for 20 to 30 minutes. Even a very small dose causes flushing of the face, a feeling of heat and a quick pulse. It often causes headache, probably due to the unreduced portion of the molecule. It is best given as a tablet of 1/200 gr. (0.3 mg.) under the tongue to dissolve slowly. It is toxic but not in the therapeutic doses. With repeated administration, tolerance is often established.

4. **SODIUM NITRITE**.—This is given internally by the mouth. It is even slower in action than glyceryl trinitrate as the absorption takes some time. The effects are more sustained which remain for $\frac{1}{2}$ to 1 hour. It is partly oxidised and excreted in the urine as a nitrate. It is used in angina pectoris, hypertension and also as diaphoretic-diuretic⁴⁶⁶.

Sodium nitrite 0.3 to 0.6 g. in 10 to 15 c.c. of water is given slowly intravenously in cyanide poisoning followed by 25 g. of sodium thiosulphate. Hopeful results have been found. (See p. 183).

5. **ERYTHROL TETRANITRATE**.—This is given by the mouth in $\frac{1}{2}$ to 2 grains doses and is slowly absorbed and decomposed in the blood into nitrite. As a consequence, its effects are more **gradual** in development. The fall in the blood pressure begins in 6 to 30 minutes and reaches the maximum in $1\frac{1}{2}$ hours and remains so for 2 to 5 hours⁴⁶⁷.

A 1% solution nitrite added to an aqueous antiseptic solution preserve the surgical instruments from rusting.

(466) R
Sod. Cit. gr. 15
Sod. Nit. gr. 1
Liq. Ammon. Acet. Fort.
min. 10
Syr. Tolu. min. 60
Aq. Camph. ad. fl. oz. 1
A diaphoretic-diuretic mixture.

(467) R
Sod. Nitris. gr. $\frac{1}{2}$
Erythrityl. Tetranit. gr. $\frac{1}{2}$
Mannitol Nitratis gr. $\frac{1}{2}$
Ammon. Hippuras gr. 1
Make into a tablet : one every
2 to 4 hours.

MANNITOL NITRATE (Not official).—In 1 gr. dose is given orally in angina pectoris and asthma : the action is less powerful but more prolonged.

[THERAPEUTIC USES OF NITRITES.]—These have been used in all diseases where the symptoms are due to sudden vascular spasm. The action is immediate, although of short duration.

In **angina pectoris**, amyl nitrite often causes the distress to disappear quickly. This is due to improvement of coronary circulation by vaso-dilatation. The effect is kept up by nitroglycerin, sodium nitrite or erythrol tetranitrate : these may be used as prophylactic also.

In **spasmodic migraine** associated with paleness of the face, the pain is often immediately relieved.

In **epilepsy**, inhalation of amyl nitrite may ward off an attack where a distinct aura gives a sufficiently early warning of its approach. It is valueless when the attack has already commenced and the face is cyanosed. The action is symptomatic and has no curative effect.

To lower **high arterial pressure** as in chronic nephritis, nitroglycerin, sodium nitrite or erythrol tetranitrate may be given 3 to 4 times daily. A certain amount of habituation usually occurs especially with nitroglycerin and an increasing dose becomes necessary. It is liable to fail in cases associated with œdema. As a matter of fact, no lasting lowering to be of definite therapeutic value is very much possible. It is useful only in an emergency, when a high blood pressure threatens the rupture of the blood vessels in the brain.

To control **bleeding from the nose** and also in **hæmoptysis**, amyl nitrite may be given by inhalation and this acts by reducing the blood pressure.

Amyl nitrite has also been given to overcome **chloroform collapse** and probably it acts by lowering the peripheral resistance and thus lessening the exertion of a weak heart.

But as in this condition the blood pressure is already low, amyl nitrite is not quite safe.

Nitrites are now used as antidote to **cyanide poisoning**. Amyl nitrite inhalation is given immediately followed by intravenous injection of sodium nitrite and sodium thiosulphate. See p. 183.

SUMMARY.—Nitrites act (i) directly on the **unstriated muscle fibres**, markedly of the arterioles and partly of the intestine, biliary passages, ureter and of the bronchioles : (a) arterial dilatation relieves pain of angina pectoris (amyl nitrite also trinitrin and sod. nitrite) : (b) lowers blood pressure (sod. nit., erythrol tetranit. and mannitol. nitrate) : (c) relieves muscular spasm of asthma and various colicky conditions (amyl nitrite and octyl nitrite) and acts as diaphoretic and diuretic (Sp. Æther. Nitros.). (ii) Forms **methæmoglobin** and sod. nitrite is given intravenously in cyanide poisoning.

Non-official Preparations

OCTYL NITRITE is prepared by the interaction of *iso*-octyl alcohol 2-ethyl hexanol), sodium nitrite and sulphuric acid. Given by inhalation

by crushing a glass pearl (like amyl nitrite) it causes vaso-dilatation and relaxation of smooth muscles: the effects are more sustained with less toxicity. A dose of 3 to 6 minims is given for angina pectoris, cardio-spasm and gastro-intestinal colic.

MUSCLE EXTRACT.—The extracts have been found occasionally useful in angiospasm. *Lacarnol* (a nucleosidic fraction from organic tissue extracts), 10 to 25 drops orally or $\frac{1}{2}$ to 1 c.c. subcutaneously, intramuscularly and intravenously, has been found useful in coronary sclerosis and angina pectoris.

PADUTIN, a pancreatic hormone, extracted from normal human urine, 1 c.c. hypodermically or 1 c.c. orally dilates blood vessels and relieves various conditions of vascular spasm. It is prescribed in hypertension, intermittent claudication, Raynaud's disease and in a slowly healing ulcer.

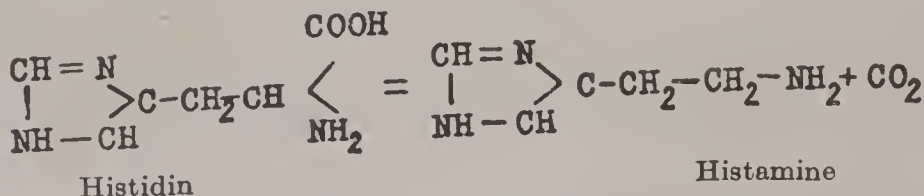
HYPOTENSYL is the active principle of *viscum* (Gui) with hepatic and pancreatic extracts in tablet, used for hypertension.

MISTLETOE.—Its preparations have some reputation in the treatment of high blood pressure. It has said to act through the vaso-motor centre without depressing the heart. The commercial products are *Guipsine*, *Drosil* and *Phyllosan* in tablets: one 3 times daily.

PRISCOL, 2-benzyl 4:5-imidazoline hydrochloride, in 25 mg. tablets, 1 c.c. containing 10 mg. ampoule and in 10% solution, is used as dilator of small blood vessels (acting on autonomic nervous system) and used in Raynaud's disease, intermittent claudication and in thrombo-angiitis obliterans.

HISTAMINE, Ergamine

Although naturally present in ergot in a small quantity, it is more commonly found where a protein is being broken into aminoacids, putrefactive bacteria being also present. Aminoacid histidine by losing CO_2 becomes histamine. It is present in the intestinal contents, in decomposing meat and also probably in injured tissues (causing symptoms of secondary shock). It has been isolated from the pyloric and the intestinal mucosa, liver, lungs, spleen and the heart.



OFFICIAL PREPARATIONS.—(i) *Histaminæ Phosphas Acidus* (*Histam. Phosph. Acid.*), Histamine Acid Phosphate, $\text{C}_6\text{H}_9\text{N}_3\cdot 2\text{H}_3\text{PO}_4$.—This is the di-acid phosphate of histamine, 4-beta-aminoethylglyoxaline, obtained from natural sources or by synthesis. Histamine is treated with phosphoric acid. Colourless, inodorous crystals, soluble at 15.5° in 4.5 of water and slightly so in alcohol (90%). **DOSE** by subcutaneous injection, 1/120 to 1/60 grain or 0.5 to 1 mg. (ii) *Inj. Histaminæ Phosphatis Acidi* (*Inj. Histam. Phosph. Acid.*), See p. 44. **DOSE**, as of Histamine Acid Phosphate. If the strength is not stated, 1/60 gr. in 15 min. or 1 mg. in 1 ml. is dispensed.

Pharmacology [and Therapeutics]

The actions of histamine are best manifested by giving it *intravenously* to an animal as a rabbit or a cat. It is moderately active by subcutaneous or intramuscular injection but relatively inactive orally. Atropine does not counteract its action.

(i) The arterioles and veinules are slightly contracted by direct action but in the carnivora, the **capillaries** are widely dilated and the result is that the blood pressure falls. The pulmonary blood vessels, however, remain contracted. Given subcutaneously or intravenously to a human being, the skin of the blush area is flushed with a rise in the skin temperature indicating dilatation of both the capillaries and the arterioles (Wakim, 1949). Some plasma escapes from the congested and unduly permeable capillaries and the blood constituents including the red blood cells, non-protein nitrogen, sugar, calcium and phosphate proportionately increase.

Injected *subcutaneously*, it causes local vaso-dilatation and exudation of plasma, also often headache (histamine headache). The place becomes congested (capillary dilatation) with a gradually widening red areola surrounding it (arteriolar dilatation): a localised wheal also forms (increased capillary permeability): Lewis's "triple response". All these appear in 5 minutes and disappear in one hour. The muscles of the bronchioles are markedly contracted and the pulmonary blood pressure rises.

(ii) Histamine causes marked **tonic contraction** of all **plain muscles** including the stomach, intestine, bronchi and the uterus, both pregnant and non-pregnant.

There is less marked action on the muscles of the alimentary canal, urinary bladder and the heart. But in toxic doses, it causes nausea, vomiting and diarrhoea by direct action on the muscles. The *pupil* is contracted from central action as it disappears under anaesthesia.

These actions are not counteracted by atropine showing that the muscles are directly affected.

(iii) The **secretion** of **many glands**, especially salivary, gastric, pancreatic and lachrymal are increased. This action is lessened by atropine: so it must be either on the ganglia or on the postganglionic nerve-endings.

(iv) It slightly depresses the **central nervous system**.

Histamine in overdose causes symptoms much resembling anaphylactic shock but the exact relationship is uncertain. In guinea-pigs and dogs in anaphylactic shock, histamine level in the blood is markedly increased.

Many tissues have an enzyme, *histaminase*, being in largest amount in the intestine and the kidneys, which in health inactivates histamine. So unless rapidly injected intravenously, histamine is often harmless.

On account of many systemic actions often causing disagreeable symptoms, histamine itself is not often used therapeutically. *Histamine Acid Phosphate* in 0.3 to 0.5 mg. dose is given subcutaneously to stimulate the gastric secretion, increasing its water, hydrochloric acid and the inorganic constituents but not pepsin. [This is of value as a *diagnostic test*. A test meal is given which is immediately followed by the injection. A part of the meal is aspirated every 20 minutes and

its acidity estimated. The increased secretion differentiates true from false achylia gastrica. This may however cause severe headache due to dilatation of the pial blood vessels and increased intracranial pressure].

Histamine is also sometimes prescribed in chronic arthritis especially in peri-articular inflammation of the hand also in myospastic and vasospastic states in 0.1 mg. dose increased to 0.5 mg. subcutaneously twice a week. This may also be given by ionization.

Histamine has also been used to determine the **circulatory velocity**. A dose of 0.1 mg. is injected into the arm or leg vein and the time taken to cause a facial flush is noted.

SUMMARY.—Histamine dilates the capillaries although moderately contracting the arterioles and venules: increases the contraction of the unstriated muscles and increases the glandular secretions. *Therapeutically*, it is used to test the gastric secretion capacity: in chronic arthritis and myospastic and vasospastic states and also to test the circulatory velocity.

LAROSTIDIN, *L-histidine monohydrochloride* and **HISTIDINE HYDROCHLORIDE** in 4% solution, 5 c.c. are given intramuscularly, daily for 3 to 4 weeks in gastro-duodenal ulcer. The hopes raised have not however been substantiated. Histamine is derived from histidine by removal of the carboxyl group.

ANTI-HISTAMINE PREPARATIONS (Not official)

The mechanism of histamine reaction had been the subject of an intensive study. The histamine effects are postulated as explosive anaphylactic reactions caused by a combination of a specific antigen with antibodies attached to fixed tissue cells resulting in somehow in the release of histamine from its bound inactive state; this condition has been found to be associated with rise in the histamine level in the tissue fluid.

The histamine released in the above way by antigen-antibody reaction, may produce response either in the *cells* releasing it or to some *distant part* of the body. Dale (1948) called the first, *intrinsic* and the second, *extrinsic histamine reaction*. The intrinsic reaction may be in the unstriated muscle as of the intestine, uterus or on the bronchioles: the extrinsic reaction may be in the skin or nose; histamine released from the skin or nasopharyngeal epithelium diffuses to the subjacent vascular system and causes urticaria or rhinitis.

Antihistamine effect may be produced by (i) slow desensitization with histamine itself, (ii) or more readily by antihistamine drugs recently introduced. These are more effective in extrinsic histamine reactions as urticaria and rhinitis and not so much in other cases. These have no action on gastric acidity. The beneficial effects are purely *palliative* and are no substitute for desensitization procedures. These antihistamines probably act by blocking the tissue receptors for histamine thereby prevent histamine from producing its customary effects.

CLINICAL USE.—Generally speaking pyribenzamine, mepyramine (Anthisan) and promethazine are more effective: *oral route* is sufficient: sometimes *local application* is helpful.

(i) Urticaria, serum sickness and dermatographisms and sometimes atopic dermatitis, contact dermatitis and some types of pruritus are treated: tablets or capsules orally and 2 to 5% ointment locally. Benadryl although less effective, relieves pruritus by its sedative effect.

(ii) Allergic rhinitis and hay fever respond well with pyribenzamine and mepyramine: locally for the intranasal oedema, Antistin-Privine solution may be used.

(iii) Gastro-intestinal allergy, migraine, erythema multiforme, allergic eye affections and certain drug eruptions: also liver extract, insulin and penicillin allergy may improve.

(iv) In acute nephritis, mepyramine may succeed.

(v) Parkinsonism and nausea and vomiting of central origin are also treated.

(vi) In bronchial asthma the results are not very promising.

DOSES.—Promethazine has prolonged action: a single dose of 25 to 50 mg. at bed time may do. Benadryl and pyribenzamine 50 mg. and antistin and mepyramine 100 mg. 2 to 4 times daily are recommended.

Histamine sensitivity has been counteracted by giving minute doses of it subcutaneously and gradually increasing. Thus 0.25 c.c. of 1 c.c. ampoule containing 0.275 mg. has been given in cephalalgia (Hoston, 1941) and also in nasal allergy, conduction deafness, asthma, dermatitis and laryngitis (Girling 1943). The effects may be more lasting.

COMMERCIAL PREPARATIONS

LERTIGON (Histamine Azoprotein). each c.c. containing 1 mg. of histamine base is used subcutaneously started with 0.01 c.c. increased every 4th or 5th day by 0.01 c.c. to 0.1 c.c. and then increased by 0.1 c.c. upto the maximum of 1 c.c.: useful in many allergic conditions as desensitizer.

ANTHISAN, mepyramine maleate, in 0.05 g. and 0.1 g. tablets: 0.025 g. in 4 c.c. elixir: 2.5%, 2 c.c. ampoules and 2% cream: effective antiallergic.

ANTISTINE (2-phenylbenzyl-aminomethyl-imidazoline) available in 0.1 g. tablets (one 3 times daily) and 0.1 g. in 2 c.c. ampoules (1 to 2 c.c. i.m. 3 times daily) is used in urticaria, eczema, prurigo, neurodermatitis, lichen planus and psoriasis.

BENADRYL (Beta-dimethylaminoethyl benzhydriylether hydrochloride) in 50 mg. capsules or as elixir containing 10 mg. in one tea-spoonful: adults are given capsules and children elixir 3 to 4 times daily. This is useful in allergic rhinitis, urticaria, angioneurotic oedema, Meniere's disease, migraine, serum sickness, dermatographism, eczema, asthma and dysmenorrhœa.

HISTADYL, thenylpyramine hydrochloride in 2% cream with cyclo-methycaine 0.5% is used in allergic rhinitis.

HISTOSTAB, 0.1 g. tablets, 0.1 g. in 2 c.c. ampoules, 2% cream and 0.5% solution with 1/4000 imidazoline compound (for eye and nose allergy).

PHENERGAN, promethazine hydrochloride in 0.01 g. and 0.025 g. tablets or elixir (each fl. dr. has 3 mg. is effective).

PYRIBENZAMINE in 50 mg. tablets, 5 mg. in 1 c.c. elixir: 50 mg. in 1 c.c., 10 c.c. vials:

SYNOFEN, dimethyl-aminoethyl-chlorobenzyl-aminopyridine in 0.025 g. tablets, ampoules 1%, 2 c.c. and ointment.

THEPHORIN, phenindamine in 25 mg. tablets and 5% ointment : does not cause sleepiness, rather insomnia.

TOXIC SYMPTOMS.—Benadryl causes sleepiness (amphetamine is given to counteract) : antistin, mepyramine and pyribenzamine may cause nausea, vomiting, colic and diarrhoea (are given after food) : promethazine may cause light headedness, ataxia and pain in the limbs.

XII. DRUGS ACTING ON THE RESPIRATORY SYSTEM

Various drugs act on the respiratory system, either by increasing or diminishing the normal physiological functions. Thus, these may either increase or diminish—

- (i) Respiratory movements.
- (ii) Contraction and relaxation of the bronchial muscles.
- (iii) Bronchial secretions : with these may be added the drugs that alter the nature and the infectivity of the bronchial secretions (*pulmonary antiseptics*).

Drugs acting on the Respiratory Movements

The normal respiratory movements are controlled by many factors. The *centre* is in the pons and the upper part of the medulla. This possesses a rhythmicity which regulates CO_2 and O_2 concentration in the blood and in the tissue.

The drugs acting *direct* through the blood or *reflexly* on the respiratory centre in the medulla, alter the respiratory movements.

Drugs acting *directly* are (i) **stimulants** as carbon dioxide, atropine, caffeine, picrotoxin, leptazol, nikethamide, ephedrine, camphor, lobeline, strychnine, cocaine, amphetamine and altered pH of blood (acidosis). (ii) **Depressants** as bigger doses of the morphine group, hydrocyanic acid, hypnotics, general anæsthetics, oxygen lack and altered pH of blood (alkalosis).

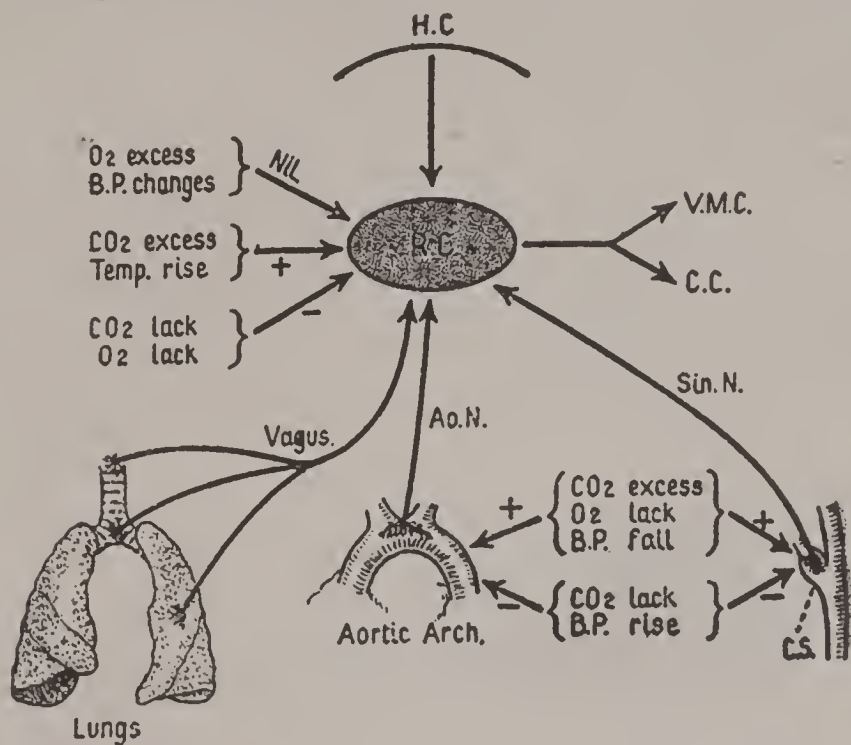
The following also in toxic doses are depressant but are of toxicological importance only.

Physostigmine, atropine, aconitine, gelseminine, cocaine, coniine, nicotine and the nitrites.

Drugs acting indirectly *reflexly* are (i) through any powerful *sensory stimulus* as from the skin as an injection of camphor or ether ; (ii) through the *nose* (the first and the fifth nerves) by a strong smell as inhalation of ammonia : (iii) through afferent *vagal impulses* from the lungs also through the *sino-aortic* nerves. The last is of indirect importance in drug action.

(i) The effect of stimulation is to increase the rate and amplitude of the respiratory movements and excite the cough reflex and that of depression is to diminish both. Therapeuti-

cally, the respiratory excitants are given in various emergencies associated with sudden respiratory failure and also sometimes for exciting the cough-reflex for favouring the expulsion of



(Wright)
Fig. 57.—Respiratory Mechanism. R.C., the respiratory centre is acted on by the higher centre (H.C.), sino-aortic (carotid sinus and aortic nerves) and pulmonary afferent impulses and also by O₂ and CO₂ concentration. It acts on the vaso-motor and the cardiac centres (C.C.).

bronchial secretions. (ii) The depressants, especially some of the opium preparations and hydrocyanic acid, are mostly used for allaying the irritating cough.

ACIDUM HYDROCYANICUM DILUTUM (*Acid. Hydrocyan. Dil.*), Dilute Prussic Acid, (Not official).

This is aqueous solution of hydrogen cyanide and contains 2% by weight of HCN. It is a colourless liquid with characteristic odour.

Dose, 2 to 5 minims or 0.12 to 0.3 ml.

Pharmacology [and Therapeutics]

The pure acid is highly poisonous and if inhaled, causes death in a few seconds. It is occasionally used for disinfecting ships and houses.

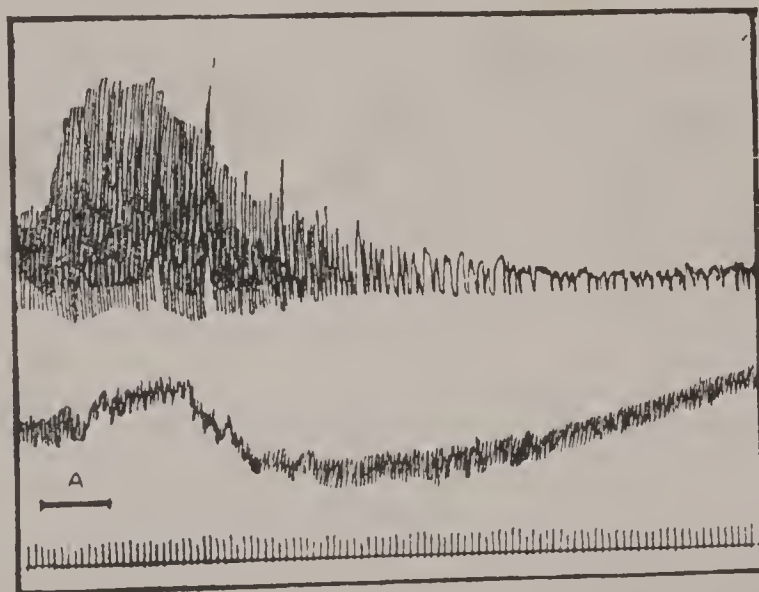
The fatal dose is 1 to 1.5 grains : so it is really less poisonous quantitatively than many of the alkaloids.

LOCALLY, Hydrocyanic acid is an **anæsthetic**. A 2% solution of it is sometimes prescribed for vomiting and pain in the stomach⁴⁶⁸ following gastritis.

In poisonous doses, Hydrocyanic acid is quickly absorbed from all mucous surfaces and even to some extent from the unbroken skin with fatal result, but in non-fatal cases, it is so quickly eliminated, as sulphocyanides which are non-toxic. that very soon all its effects disappear.

The normal gaseous exchange in the body ceases. During its passage through the capillaries, the blood does not as usual lose oxygen and even in the veins, it retains the same bright red colour. This is due to the loss of power of the tissues to absorb oxygen from the blood. But as death approaches and respiration becomes feeble, it assumes venous character.

The effects of lessened tissue oxidation are an increase of sugar and lactic acid in the blood and more nitrogen, sulphur and urea in the urine.



(After Dixon)
Fig. 58.—At A, hydrocyanic acid was given by inhalation. The respiration (upper curve) and blood pressure (lower curve) were raised (medullary stimulation) followed by depression, afterwards recovery. Time is marked in second.

RESPIRATION.—In therapeutic doses, it is only slightly depressant to the respiratory centre, **diminishing the cough reflex.** [It is sometimes used for allaying irritating cough⁴⁶⁹ combined with opium especially codeine in the form of a cough linctus. By itself, it is not of much therapeutic value].

(468) ℞
Acid. Hydrocyan. Dil. min. 3
Liq. Bism. min. 20
Sod. Bicarb. gr. 20
Liq. Morph. Hydrochlor. min. 8
Sp. Chlorof. min. 8
Aq. Menth. Pip. ad. fl. oz. 1
(Lucas).

For vomiting of gastritis.

(469) ℞
Bromoform. min. 2
Menthol gr. $\frac{1}{2}$
Acid. Hydrocyan. Dil. min. 3
Syr. Codein. Phosph. min. 30
Syr. Tolu. ad. min. 60
Linctus. For irritable cough.

Given in minute doses, as 1 mg. of sodium cyanide, intravenously to a rabbit it markedly stimulates the respiratory centre, increasing the rate and the depth of respiration. With a bigger dose, the rhythm is made irregular but with a nonfatal dose, this becomes normal again.

Minute doses of sodium cyanide have been tried therapeutically intravenously in respiratory failure. As the optimum dose is difficult to adjust, it is hardly safe.

CIRCULATION.—With a very small dose, **vaso-motor** and the **cardiac centres** are stimulated. The blood pressure rises and the pulse is slowed. But this action is of short duration. With a bigger dose, the centres and the heart muscles are depressed and death takes place from respiratory failure.

CENTRAL NERVOUS SYSTEM is at first stimulated and then paralysed causing convulsion, followed by generalised muscular paralysis and death.

If the dose is not immediately fatal, after a brief prodromal stage, pain in the region of the heart, feeling of constriction in the chest, dyspnoea and respiratory spasm ensue. The respiratory movements are infrequent and laboured and death ensues from respiratory failure. All these very quickly follow one another and are due to **paralysis** of the **respiratory centre** in the medulla. If the patient can tide over one hour, the recovery is usually rapid and complete.

SODIUM or **POTASSIUM SULPHOCYANATE** in $2\frac{1}{2}$ to 5 grains doses, 2 to 3 times daily, is occasionally given for high blood pressure but there is danger of cumulative toxicity.

RHODAN-CALCIUM-DIURETIN, in tablets of $7\frac{1}{2}$ grs. of calcium diuretin and $1\frac{1}{2}$ grs. of potassium sulphocyanate, is sometimes useful in hypertension.

POTASSIUM THIOCYANATE is also similarly used in $1\frac{1}{2}$ gr. doses t.d. for a week: the thiocyanate concentration in the blood is kept between 8 to 12 mg. % by subsequent administration in smaller doses; this method is safe and more effective.

PRUNUS SEROTINA (*Prun. Serot.*), Virginian Prune Bark, Wild cherry bark

The bark of *Prunus serotina*, the wild cherry, is obtained as reddish brown and smooth curved pieces often covered with a smooth, thin, reddish-brown to brownish black papery cork frequently exfoliating: marked with transversely elongated lenticels and inner surface is reddish brown, finely striated or fissured: fracture is granular having a bitter aromatic astringent taste. It grows in North America.

Its active principles are *amygdalin* and a ferment *emulsin* which in contact with water produce hydrocyanic acid. It also contains a bitter principle, resin etc.

Amygdalin + water = Dextrose, hydrocyanic acid and benzaldehyde.

PRUNI SEROTINÆ PULVIS (*Prun. Serot. Pulv.*): light brown powder of virginian prune bark.

Syrupus Pruni Serotinæ (*Syr. Prun. Serot.*). Syrup of wild cherry. See p. 55.

Dose, 30 to 120 minims or 2 to 8 ml.

The chief active principle of Virginian Prune Bark is *amygdaline* which, when mixed with water, yields hydrocyanic acid and its action is chiefly due to this. It depresses the respiratory centre in the medulla [and is frequently prescribed to relieve hacking cough in the form of syrup, often combined with an opium preparation⁴⁷⁰].

2. Drugs acting on the Bronchial Muscles

The drugs of this group either increase or lessen the bronchial spasm and are called *broncho-constrictors* or *broncho-dilators*.

BRONCHO-CONSTRICTORS : these are (a) the parasympathomimetic drugs as physostigmine, pilocarpine, acetylcholine and also nicotine, coniine and lobeline in the first stage.

(b) Those acting directly on bronchial muscles are barium, veratrine, histamine and posterior pituitary extract. But these are of no therapeutic value.

BRONCHO-DILATORS are often sympathomimetic drugs. These by relaxing the bronchial spasm, cause dilatation of the bronchi and are frequently used for the relief of asthmatic attacks.

(i) Those acting directly by (a) *depressing* the vagal endings : drugs of the belladonna group : (b) *depressing* the vagal ganglia as a big dose of nicotine also lobelia and grindelia : (c) *depressing* the bronchial muscles as nitrites, benzyl benzoate, theophylline and papaverine also antihistamine preparations (p. 673). (d) by *stimulating* the sympathetics as adrenaline, ephedrine and to a less extent amphetamine.

Newer synthetic preparations with sympathomimetic actions are also getting popular (see p. 623 and 626).

(ii) Those acting as **general nerve depressant** as bromides, barbiturates, morphine, chloroform and hyoscine. Although chloral hydrate, opium and cannabis indica have the property of relaxing muscular spasm, these are seldom used therapeutically as bronchodilators.

Of these (a) chloroform, amyl nitrite and the fumes of burnt stramonium and potassium nitrate are given by *inhalation* : (b) suprarenal extract and atropine occasionally morphine (in cardiac asthma) by *hypodermic injection* and (c) the rest *orally* to relieve broncho-spasm of asthma.

(470) B

Chlorof. min. 1

Tinct. Opii Camph.

Syr. Prun. Serot.

Oxymel. Scill.

Tinct. Seneg. aa. min. 15

Linctus : for irritable cough.

BENZYLIS BENZOAS (*Benzyl. Benz.*), Benzyl Benzote,
Spasmodin, $C_6H_5.CO.OCH_2.C_6H_5$

Benzyl benzoate may be prepared by esterification of benzyl alcohol with benzoic acid : contains no less than 99% of $C_{14}H_{12}O_2$.

Colourless crystals or an oily liquid with a faint aromatic smell and sharp burning taste. Insoluble in water, soluble in alcohol (90%), chloroform and in solvent ether : insoluble in glycerin.

APPLIED EXTERNALLY, it is an **antiseptic** and **antiparasitic** [and is recently found successful in the treatment of scabies⁴⁷¹. After a hot bath using plenty of soap with vigorous scrubbing so as to open out the burrows of the parasites, benzyl benzoate emulsion (25%) is applied into the whole body : a second application of the emulsion is frequently made a little after when the first is dry. When fully dry, the patient is dressed up. After 24 hours, another bath may be given and a second application but one day's treatment may be sufficient. The clothes should be sterilized by boiling]. Benzyl benzoate is the principal constituent of balsam of Peru which is also used for scabies.

TAKEN INTERNALLY it relieves the spasm of all **unstripped muscles** as of the bronchi, alimentary canal, gall-bladder, urinary bladder, uterus and of the blood vessels. [It is administered in 3 to 5 minims capsules or in 20% emulsion in bronchial asthma, intestinal, biliary and renal colics, spastic constipation and in dysmenorrhœa]. The results are not in every case very satisfactory.

BENZYL ACETYL SALICYLATE and BENZYL SUCCINATE⁴⁷² (Not official) are also used in the same way as antispasmodic.

TETMOSOL (tetra-ethylthiuram monosulphide, in 25% solution in industrial alcohol with 10% polyglyceryl ricinoleate), diluted with 2 to 3 times of warm water is applied in the same way as benzyl benzoate for scabies.

BENZOPED is an aqueous emulsion of benzyl benzoate, D.D.T. and benzocaine : used for scabies and lice without danger of skin irritation.

EURAX, Crotonyl-N. Ethyl-O-Toluidine, 10% ointment is applied after bath over the whole body and repeated at bed time : bathed in the next morning and changed clothes : affective in scabies without local skin irritation.

KWELL, Hexachlorocyclohexane is a satisfactory scabicide : one application is usually sufficient and causes no skin irritation.

3. Drugs increasing or decreasing the Bronchial Secretions

The drugs that *expel* the bronchial secretions are called **expectorant** (L. *ex*, out and *pectus*, breast). These are largely used in many conditions either simply to expel or increase and

(471) R

Benzyl. Benz. 25
Lanett. wax s.x. 2
Aq. ad. 100

This resembles *Ascabiol*, *Scobanol* or *Enzol* proprietary preparations.

(472) R

Benzyl. Succ. gr. 5
Papaver. Sulph. gr. $\frac{1}{2}$

Put up in capsule. One every 2 to 4 hours as antispasmodic.

expel, the bronchial secretions. These act (a) by increasing the secretion, (b) making the secretion thinner and less viscous (c) or/and by inducing cough.

The anatomical points are (a) a *cough centre* in the medulla, close to the vomiting centre : (b) *afferent vagus* in the tracheo-bronchial mucous membrane, (c) *efferent vagus* and *efferent sympathetic* in the glands and muscles : these regulate the bronchiolar exudates, production of cough reflex and expectoration. The drugs concerned may be grouped as follows :

(i) *Drugs that increase all glandular secretions*, also increase the bronchial secretion and are therefore partly expectorants, as pilocarpine. But such drugs cannot be used as expectorants for their disadvantageously increasing, at the same time, all secretions of the body which are not required.

(ii) *Drugs that act reflexly through the vagus*.—The same nerve vagus, supplies both the stomach and the bronchial mucous membrane. The drugs which irritate the stomach reflexly stimulate the bronchial secretion and hence all emetics in subemetic doses are expectorant, as ammonium bicarbonate and chloride, antimony salts, ipecacuanha, squill and senega. Apomorphine in very small doses as gr. 1/80 has the same action.

(iii) Certain drugs, taken orally, are absorbed into the blood and *in the process of elimination*, are carried to the bronchiolar mucous membrane to produce direct effect there on the bronchiolar glands. These are salines as carbonates, bicarbonates also to some extent, chlorides, acetates and citrates : ammonium chloride, potassium iodide : essential oil as oil of turpentine (also terpine hydrate), camphor, balsam of tolu, cubebs, sandal wood oil, eucalyptus oil and ammoniacum : also benzoates and benzoic acid and to a less extent, squill and senega. The action depends on either local salt action or on a mild irritation in the process of excretion.

Some of these are mild *antiseptics* as volatile oils, benzoates, creosote or guaiacol : these taken orally are absorbed and carried to the bronchiolar mucous membrane and claimed to have some antiseptic action : but these do not attain a concentration which would be sufficient for any lethal action on the infective organisms there. These drugs and also potassium iodide are yet called "**Pulmonary antiseptics**".

Certain volatile oils, benzoin and creosote are given by inhalation also. Although slightly antiseptic to the upper respiratory passages, these are more useful as **deodorants** in conditions of foetid expectoration.

More powerful pulmonary antiseptics are *sulphonamides* specially in pneumococcal and streptococcal infections : also *penicillin* and in some cases *streptomycin* : other antibiotics and P.A.S. are also establishing similar claims. (See p. 381).

There are also terms, **STIMULATING** and **SEDATIVE EXPECTORANTS**. The former again are called the *irritating*

expectorants which in the process of excretion, irritate the bronchial mucous membrane and increase expectoration. The aromatic expectorants as volatile oils also creosote preparations, senega and squill are included in this group.

The *sedative expectorants* are those that soothe the acute inflammation, mainly by stimulating the secretion of protective mucus. In this group are included the *nauseating expectorants* (ipecacuanha and antimony); *saline and alkaline expectorants* (ammonium chloride, ammonium bicarbonate, iodides, sodium bicarbonate and citrates and acetates) and *demulcents* as gum acacia, syrups and glycerin.

There is another group again. Opiates (especially codeine), hydrocyanic acid, bromides and chloroform by acting on the respiratory centre, depress the cough reflex and are used for the relief of irritating cough with scanty expectoration. These may be called the *anodyne expectorants*.

But such classifications are arbitrary and not necessary for any therapeutic grouping as a member of one group is often combined with that of another.

THERAPEUTIC USES OF EXPECTORANTS

Coughing is thus the normal physiological reflex mechanism needed to keep the bronchial passages free of unnecessary secretions and unless *excessive* or *unproductive*, which exhausts the strength of the patient, no medication is necessary. The secretions are from the tracheobronchial mucous membrane which has many glands richly supplied with blood vessels. The excessive secretion in most cases is due to inflammation or local irritation on the mucous membrane (from various respiratory diseases) and in certain cases from venous stasis (congestive circulatory failure). For the former, different expectorants are usually sufficient and for the latter, drugs acting on the cardiovascular system are also necessary.

Sometimes there is a removable exudate and the cough is followed by expectoration: this is called *productive cough*. But in other cases as in acute inflammation of the bronchial mucous membrane (acute bronchitis) or in any irritation of vagal endings outside the bronchial tree, there is no exudate to come out: although cough is caused which may even be persistent and troublesome, it is *nonproductive*. Drugs used in one condition is different from the same of the other.

(i) If cough is due to an *irritable condition of the upper respiratory passages* without any expectoration, the drugs used are: (a) demulcents as syrups, glycerin and gum: (b) local applications as sprays containing menthol, camphor, chlorbutol and volatile oils (also ephedrine and amphetamine if much local congestion) dissolved in a suitable vehicle as water or in liquid paraffin: (c) inhalation of volatile antiseptics with steam: (d) paints and gargles of anodyne, antiseptic or

astringent lotions : (e) also sedatives as diamorphine, codeine or camphorated tincture of opium, prunus serotina and bromides.

(ii) Cough may be due to *unduly sticky sputum* : drugs increasing the bronchial secretions as alkaline salts, iodides, emetics in subemetic doses, saponins and volatile oils are prescribed.

(iii) Cough may be due to *unduly copious sputum* : firstly, drugs exciting the cough reflex as irritating expectorants are prescribed : in children, an emetic may be given. Afterwards calcium (to lessen capillary exudation) and belladonna and opiates (to lessen bronchiolar secretion) are indicated.

SENEGA (*Seneg.*), Senega Root

Greyish or brownish yellow slender roots of *Polygala Senega*, 2" to 8" (5 to 20 cm.) long, 0.12 to 0.24" (3 to 6 mm.) wide with knotty crown bearing the bases of numerous slender stems tapering below : often curved or contorted without much branching and occasionally transversely wrinkled. Available from North America.

It contains *senegin*, a glucoside, identical with Saponin.

SENEGÆ PULVIS (*Seneg. Pulv.*) : grey powder of senega root.

OFFICIAL PREPARATIONS.—(i) *Extractum Senegæ Liquidum* (*Ext. Seneg. Liq.*), See p. 40. DOSE, 5 to 15 minims or 0.3 to 1 ml. (ii) *Infusum Senegæ Concentratum* (*Inf. Seneg. Conc.*), See p. 41. This is 7 times stronger than the fresh infusion. DOSE, 30 to 60 minims or 2 to 4 ml. (iii) *Infusum Senegæ* (*Inf. Seneg.*), See p. 41. DOSE, $\frac{1}{2}$ to 1 fl. oz. or 15 to 30 ml. (iv) *Tinctura Senegæ* (*Tinct. Seneg.*), See p. 60. DOSE, 30 to 60 minims or 2 to 4 ml.

CHINENSIS is the dried root of *Polygala Chinensis*, Senega of IND. PHARM. LIST. May be used for senega.

QUILLAIA (*Quill.*), Quillaia bark

These are flat pieces, varying considerably in length and width, of the bark of *Quillaja Saponaria*. Outer surface is brownish-white or reddish brown longitudinally streaked or coarsely reticulated : inner surface is smooth, hard, white or yellowish white. Fracture is splintery and laminated, the broken surface showing glistening points of calcium oxalate crystals. Taste is acrid and astringent. Vigorously shaken with water it forms copious persistent froth due to saponin, a glucoside. It grows in Chile.

QUILLAIA PULVIS (*Quill. Pulv.*) : Pale buff powder with a pink tinge.

OFFICIAL PREPARATION.—*Extractum Quillaiæ Liquidum* (*Ext. Quill. Liq.*), See p. 40. Several other plants contain saponins or sapotoxins as *Saponaria Officinalis*, *Cyclamen Europeum*, *Argostemma githago* and the like : closely allied to saponins is *Solanine* found in some varieties of solanum. But these are of no therapeutic value.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, *Senegin* is a powerful local irritant to the skin and much more so to the mucous membranes. Thus when inhaled in the form of a powder, it causes violent irritation of the nose leading to sneezing and cough.

TAKEN BY THE MOUTH, it produces the same irritant action on the stomach and intestine, causing vomiting, diarrhoea, colitis and finally collapse and death. In a much smaller dose, (as 20 or 30 minims of the tincture), this acts as expectorant⁴⁷³⁻⁴⁷⁶ to increase the bronchial secretions and their final expulsion. The action is mainly from the gastric reflex. Probably a very minute quantity is also absorbed which acts directly on the bronchial mucous membrane. Its irritant properties make it unsuitable during the acute stage of pulmonary diseases but is helpful in sub-acute or chronic bronchitis and also during the resolution stage of pneumonia to clear out the bronchial tree.

From oral administration it has no definite action on the circulation as very little of it is absorbed. Given subcutaneously or intravenously, it sets up severe vomiting, diarrhoea and acute nephritis. It dissolves lecithin and combines with cholesterolin. The red blood corpuscles are broken down and the coagulation of blood is retarded and finally the heart stops and respiration fails.

QUILLAIA on account of its saponin contents has a similar action but is seldom used therapeutically. It is used in Pharmacy to emulsify oils. (p. 73.)

BENZOINUM (*Benzoin.*), Benzoin, Gum Benjamin, Loban

A balsamic resin obtained by incising the stem of *Styrax Benzoin* and of *Styrax paralleloneurus*, obtained from Sumatra or *Styrax tonkinensis* from Siam.

Whitish or reddish tears embedded in greyish brown or reddish brown matrix, (*Sumatra benzoin*) or flattened tears, irregularly prismatic, fusiform or ovoid : freshly fractured surface is milky white (*Siam benzoin*) : with an agreeable balsamic odour and slightly acrid taste. It contains between 19 to 29% of free balsamic acids and 30 to 60% of total balsamic acids. It contains (i) Benzoic acid, (ii) Resins, (iii) A trace of cinnamic acid and (iv) Volatile oil.

OFFICIAL PREPARATIONS.—(i) *Adeps Benzoinatus* (Siam Benzoin), See p. 36. (ii) *Tinctura Benzoini Composita* (*Tinct. Benzoin. Co.*), Friars' balsam. See p. 59. *Sumatra Benzoin*.

(473) R
Pot. Iod. gr. 2
Tinct. Scill. min. 5
Sp. Ammon. Aromat. min. 20
Vin. Antim. min. 8
Inf. Seneg. Rec. ad. fl. oz. 1
Mix. For subacute bronchitis.

(474) R
Tinct. Seneg. min. 30
Liq. Ammon. Acet. Dil. min. 60
Sp. Ammon. Aromat. min. 20
Syr. Tolu. min. 60
Aq. Camph. ad. fl. oz. 1
For subacute and chronic bronchitis.

(475) R
Tinct. Seneg. min. 15
Tinct. Scill. min. 5
Tinct. Bellad. min. 3
Tereben. min. 5
Tinct. Opii Camph. min. 30
Aq. ad. fl. oz. 1 (Lucas)
For chronic bronchitis.

(476) R
Pot. Iod. gr. 10
Ammon. Carb. gr. 5
Tinct. Lobel. Æther.
Sp. Chlorof. aa. min. 20
Tinct. Ipecac. min. 10
Inf. Seneg. Rec. ad. fl. oz. 1
For chronic asthma.

1. **ACIDUM BENZOICUM** (*Acid. Benz.*), Benzoic acid, $\text{HC}_7\text{H}_5\text{O}_2$. This is benzene (C_6H_6) minus H, plus COOH .

Benzoic Acid is either obtained from benzoin or prepared synthetically : contains not less than 99.5% of $\text{C}_7\text{H}_5\text{O}_2$.

Light, nearly colourless almost inodorous crystalline needles or plates, soluble 1 in 450 of cold water, but readily in solution of alkalies, fixed and volatile oils, in 3 of alcohol (90%), and in chloroform, 7 parts. Sodium phosphate and borax favour its solution.

OFFICIAL PREPARATION.—*Tinctura Opii Camphorata* (*Tinct. Opii Camphor.*), See p. 59. It contains in 60 min. 1/30 gr. of anhydrous morphine (0.05%). **DOSE**, 30 to 60 minims or 2 to 4 ml.

2. **SODII BENZOAS** (*Sod. Benz.*), $\text{NaC}_7\text{H}_5\text{O}_2$.

Prepared by neutralising benzoic acid with sodium carbonate.

A white amorphous, granular or crystalline powder with a faint odour of benzoin and unpleasant sweetish saline taste. Soluble in 2 of water and feebly in alcohol 90%. It contains not less than 99% of $\text{C}_7\text{H}_5\text{O}_2\text{Na}$ of the substance dried at 110° .

DOSE, 5 to 30 grains or 0.3 to 2 gramme.

INCOMPATIBLES.—Liquor potassi, acids and ferric salts.

Pharmacology [and Therapeutics]

The chief constituent of this balsamic resin, Benzoin is benzoic acid.

APPLIED EXTERNALLY, Benzoic acid is a powerful **antiseptic**^{477, 478} so much so that one per cent solution is sufficient to inhibit the bacterial growth. But its salts are not so active.

The compound tincture is a popular dressing for superficial wounds. It is specially used for sealing clean wounds, [being applied on a piece of cotton wool which, on drying, forms a crust good enough to keep off all infective agents. Along with iodoform, it forms a stimulating application for indolent ulcers and sinuses]. Benzoic acid makes throat lozenges ($\frac{1}{2}$ gr. each).

In pharmacy, benzoin is used as preservative for lard, benzoinated lard being a popular ointment basis. It is also used as food preservative.

TAKEN INTERNALLY, by the mouth benzoic acid acts as an **antiseptic** to the alimentary canal but a large dose is irritant. It is quickly absorbed as a benzoate.

Benzoic acid and its salts are conjugated in the liver with glycine, finally changed into hippuric acid, but a part of it remains unchanged. If the dose is large, a part combines with glycuronic acid also. All these are excreted in the urine.

(477) **R**
 Acid. Benz. gr. 10
 Ol. Menth. Pip.
 Ol. Cinnam. aa. min. 2
 Tinct. Kramer. min. 15
 Saccharin. Solub. gr. 5
 Alcohol 90% fl. oz. 1
 30 drops in $\frac{1}{2}$ tumbler of water
 for gargle.

(478) **R**
Whitfield ointment
 Acid. Benz. gr. 10
 Acid. Salicyl. gr. 15
 Paraff. Moll. gr. 120
 Ol. Cocois Nucifer.
 ad. fl. oz. 1
 Ung. For tinea cruris.

LIVER FUNCTION TEST.—The amount of hippuric acid excreted in the urine after oral administration of 4 g. of sodium benzoate has formed the basis of *liver function test*: a normal person should excrete in 4 hours not less than 3.2 g. of hippuric acid. If 1.77 g. of sodium benzoate is given intravenously, not less than 1 g. should be excreted in 1 hour.

This test is unsuitable in a case of renal disease.

For internal administration, ammonium or sodium benzoate is more frequently preferred to benzoic acid.

These are excreted mainly in the urine and to a less extent in the bronchial secretion, sweat and in saliva.

The urinary acidity slightly increases, ammonium benzoate being more powerful. A benzoate is thus a **urinary disinfectant**. [It was prescribed in various septic conditions of the kidneys and the bladder but now not so much used]. In addition, it is slightly **diuretic**^{479, 480}.

Further, as it is excreted with the bronchial secretion, it is a mildly **antiseptic expectorant**^{481, 483}. [It is given by the mouth in chronic lung diseases especially if associated with foetid expectoration. The compound tincture is given as an inhalation with steam for acute inflammatory conditions of the upper respiratory passages].

On the **metabolism**, it has an action somewhat resembling the salicylates, increasing the nitrogenous elimination by the kidneys but lessening that of uric acid and also acting as a feeble antipyretic. The polymorphonuclear leucocytes are increased.

In therapeutic doses, it has not much action on the *central nervous system*.

SUMMARY.—Benzoic acid is an antiseptic and deodorant and the compound tincture is often used. *Internally*, it is an *acidifier of the urine* and disinfectant also a mild *expectorant*. It is excreted mainly as hippuric acid, the amount being the test for liver efficiency.

(479) R
Hexamin. gr. 10
Ammon. Benz. gr. 15
Sp. Chlorof. min. 10
Aq. ad. fl. oz. 1
(Royal Northern)

For cystitis.

(480) R
Hexamin. gr. 7½
Ammon. Benz. gr. 10
Tinct. Hyoscy. min. 30
Inf. Uvæ Ursi Rec. ad. fl. oz. 1
Urinary disinfectant.

(481) R
Menthol. gr. 10
Ol. Eucalypt. min. 60
Tinct. Benz. Co. min. 120
Mag. Carb. Lev. gr. 30
Aq. ad. fl. oz. 2

A few drops in Maw's inhaler for inhalation.

(482) R
Creosot. Carb. min. 10
Mucil. Acac. q.s.
Sod. Benz. gr. 10
Tinct. Seneg. min. 30
Syr. Tolu. min. 60
Aq. ad. fl. oz. 1

For bronchiectasis.

(483) R
Pot. Acet. gr. 15
Liq. Ammon. Acet. Dil. min. 60
Ammon. Benz. gr. 10
Tinct. Ipecac. min. 10
Syr. Tolu. min. 60
Aq. Camphor. ad. fl. oz. 1
For sub-acute bronchitis.

Non-official Preparations

METHYL HYDROXYBENZOATE in 0·1 to 0·2% solution is a *preservative* of pharmaceutical preparations of aqueous nature.

PROPYL HYDROXYBENZOATE in 0·05% of alcoholic solution is used as a *preservative* for pharmaceutical preparations. It is also used as *anti-oxidant* in fats and oils.

CRYOGENINE, metabenzamine-semicarbazide, is an antipyretic, especially in tuberculosis.

Dose, 3 to 20 grains (soluble in 100 of water).

AMMONII BENZOAS, $\text{NH}_4\text{C}_7\text{H}_5\text{O}_2$: Dose, 5 to 15 grains. Used as urinary antiseptic in pyuria with alkaline urine.

AMMONIUM and SODIUM HIPPURATE.—Solvents for urates and also reducers of blood pressure.

Dose, 5 to 30 grains (soluble in water).

SILAJATU.—A bituminous product, obtained from the lower Himalayan hills during the summer months. It contains a large proportion of benzoic and hippuric acids also small quantities of iron, magnesium, calcium and silica. It is frequently used in Ayurveda for urinary and respiratory diseases.

ADHATODA VASICA (*Vasaka*).—This is a well-known Ayurvedic medicine largely used as *expectorant*. The plant grows extensively in the plains of India. IND. PHARM. LIST has *Extractum Vasakæ Liquidum* : *Vasaka* extracted with 60% alcohol. Dose, 15 to 30 min. or 1 to 2 ml. and *Syrupus Vasakæ* (liquid ext. with an equal part of syrup and a little glycerin). Dose, 30 to 60 min. or 2 to 4 ml.

Vasaka contains an alkaloid (*vasicine*) and a volatile oil and probably the former is the active principle. The fresh juice or an alcoholic extract may also be used. It liquefies the sputum which is coughed up more easily and it has sedative and broncho-dilator effects⁴⁸⁴.

COCILLANA BARK, contains 2·3% of a resin: the extract or syrup is used as an *expectorant* often in combination with other expectorants⁴⁸⁵.

XIII. DRUGS ACTING ON THE ALIMENTARY SYSTEM

The drugs acting on the *alimentary system* may be classified as follows :

- (i) Those modifying the activity (*stimulation or depression*) of the various GLANDULAR SECRETIONS.
- (ii) Those influencing the activity of the MUSCLES of the different portions (motor function).
- (iii) Those acting on the GASTRO-INTESTINAL CONTENTS as antiseptics, digestants and adsorbents.

The detailed actions of most of the drugs of this group have already been discussed under different headings and are not repeated here.

(484) R
Codein. Phosph. gr. 2
Syr. Prun. Serot. min. 120
Tinct. Ipecac. min. 40
Syr. Vasak. c. Tolu ad. fl.
oz. 1

One tea spoonful, repeated, for irritating cough.

(485) R
Pot. Antim. Tart. gr. 1/40
Codein. Phosph. gr. 1
Ext. Cocill. Liq. min. 8
Ext. Euphorb. Liq.
Tinct. Scill. aa. min. 20
Syr. Tolu. ad. fl. oz. 1
Syr. Cocillana Co., dose one tea-spoonful repeated.

A. Drugs acting on the Glandular Secretions of Mouth

(1) INCREASING THE SALIVA (sialogogues) :

- (i) *Reflexly*, through sight, smell and taste of a palatable food.
- (ii) Stimulation of *afferent nerve endings* in the mouth as by aromatics, pungents, bitters, acids, alcohols, chloroform, ether and any substance having a strong taste, pleasant or unpleasant.
- (iii) *Mechanical Stimulation* as by rubber or gelatin pastilles, kept in the mouth.
- (iv) By *stimulation of the para-sympathetics*, as by choline group, physostigmine, pilocarpine, nicotine and also emetics in subemetic doses as tartar emetic or ipecacuanha.
- (v) By drugs *excreted into the saliva*, as iodides and mercurials.

Usual food substances cause secretion of viscid saliva and dry or irritant substances, of copious watery saliva.

(2) DIMINISHING THE SALIVA :

- (i) Astringents as tannic acid, iron salts or alum.
- (ii) Drugs of the atropine group by paralysing the para-sympathetics.
- (iii) Opium and its alkaloids.

STOMACH

(1) DRUGS INCREASING THE GASTRIC SECRETIONS :

These are called **stomachics**. These act *reflexly* from psychic effect (the sight of a palatable food), by the *stimulation of the nerves* of the mouth and throat, (sialogogues) and also *directly* on the glands of the stomach. The latter are as follows—

- (i) Peptones, meat extracts, histamine also probably ventriculin.
- (ii) Drugs having mild irritant action on the stomach wall, as aromatics, moderately pungent substances, dilute alcohols, hypertonic salt and sugar solutions.
- (iii) Alkalies in moderate doses before food but the action is probably indirect.
- (iv) Drugs exciting the parasympathetic (vagal endings), as pilocarpine.

(2) DRUGS DIMINISHING THE GASTRIC SECRETIONS :

- (i) Inhibition from psychic reflex, as strong emotion.
- (ii) Fats and fixed oils.
- (iii) Local astringents as tannic acid or alcohols in concentrated form.
- (iv) Strong acids and alkalies. Hydrochloric acid in over 0.2% concentration inhibits the gastric secretion.

- (v) Paralysis of the parasympathetic (the vagal endings), as by atropine.

Antacids act mainly by neutralising excessive gastric secretions especially the hydrochloric acid. A normal person secretes about 5 grms. of hydrochloric acid : this can be neutralised by milk (1.5 litres), magnesium oxide or silicate (3 g.), magnesium and calcium carbonates (7 g.), sodium bicarbonate (12 g.) and bismuth oxycarbonate (136 g.), (Clark). Hydroxides of calcium and magnesium are antacids of moderate intensity.

Aluminium hydroxide and mucin are acid adsorbent.

(i) Antacids are used mainly for the treatment of *gastro-duodenal ulcer*, a condition associated with excessive secretion of hydrochloric acid in the stomach. The acid is neutralised by (a) frequent small feed mainly of milk and slops, (b) acid adsorbents as aluminium hydroxide (p. 141) and magnesium trisilicate (p. 214) : direct alkalies are avoided. Aluminium hydroxide is slightly constipating and mag. trisilicate is laxative : one or other or both combined may be used. (c) Secretion is lessened by atropine sulphate 1/100 grain before 8 A.M. and 8 P.M. feeds and 1/50 gr. at bed time and olive oil $\frac{1}{2}$ ounce before each of the three feeds.

(ii) Antacids are also used in *gastric fermentation* and *gastritis* : these are given before food followed by dilute hydrochloric acid, vitamin B Complex and pepsin after food. Bulky carbohydrate meals are avoided.

NEUTRAL MUCIN, prepared from pig's stomach is antacid with high combining power for the acid. It does not excite gastric secretion, is soothing and protective and does not disturb the acid-base balance.

It was prescribed in gastro-duodenal ulcer : half ounce (15 gm.) is given every 2 hours or as required, between 8 a.m. and 10 p.m., the average daily dose being 80 to 100 gm. (Fogelson 1932). Tufts (1932) combined it with milk and cream which increased the palatability. This failed to be much popular.

INTESTINE

The intestinal ferments are seldom very much increased or diminished independently, these being mainly dependent on the gastric hormone. The drugs that increase the gastric also increase the intestinal secretions.

B. Drugs acting on the Muscular Movements

STOMACH

The gastric peristalsis is accelerated by most cathartics, aromatic bitters, volatile oils, alcohols in small doses, also by strychnine, pilocarpine, nicotine, ergotoxine and digitalis.

The reverse peristalsis is excited by drugs called **emetics**.

In the act of vomiting, the pyloric opening of the stomach contracts the cardiac opening relaxes and by the simultaneous contraction of the diaphragm and abdominal muscles, the contents of the stomach are thrown out.

EMETICS

Drugs are used as emetic either for expelling any harmful agent from the stomach as for the treatment of poisoning or a foreign body from the throat and lungs and occasionally the bronchial secretions, especially in children who cannot expel these by coughing.

These act either on (i) *the centre* in the medulla or (ii) *the vagal endings* in the wall of the stomach. The drugs that act centrally, do so with a much smaller dose when given subcutaneously than by the mouth. Whereas the drugs with local action on the stomach, act better and quicker when given by the mouth.

The following drugs are commonly used.—

(i) Acting on the *medullary centre*.—Apomorphine subcutaneously.

(ii) *For local action* on the gastric mucous membrane.—Sodium chloride in hypertonic solution, ammonium bicarbonate, salts of heavy metals (more commonly zinc sulphate, copper sulphate, alum, antimonium tartrate), ipecacuanha powder (or emetine) and mustard powder and even a copious drink of warm water.

The *local* emetics, with local action except warm water and saline solution are all irritants. If they fail to act, they may damage the gastric mucous membrane by direct action. So in a case of poisoning, either a stomach wash or a central emetic is more desirable.

Morphine may cause emesis by exciting the medullary centre and the splanchnic ganglia especially in susceptible persons. This action is best shown if the drug is given intravenously or in a big dose subcutaneously. By its local action on the peripheral nerve-endings of the alimentary canal, it diminishes the gastric contractions (although constricts the sphincters) and acts as anti-emetic.

Digitalis in toxic doses is an emetic which thus is an indication of its over action.

ANTI-EMETICS

These are the drugs having sedative action either on the centre in the medulla or on the peripheral vagal endings in the stomach. A large number of drugs in one way or the other controls vomiting but the following are more commonly used :

(i) *Acting locally on the stomach*.—

Bismuth salts, kaolin, creta (these act by forming a bland coating), ice, cocaine group especially the insoluble preparations (p. 579), CO₂ (as an effervescent mixture), hydrocyanic acid, chlorbutol and demulcents. Also minute doses of iodine and ipecacuanha (as drop doses of weak solution of iodine and tincture of ipecac.), carbolic acid, creosote, camphor, menthol,

mercury as fractional doses of calomel, arsenic, alcohols, chloroform and ether.

(ii) *Acting by depressing the vagal centre.*—

Opium, bromides, hydrocyanic acid, chloral group (especially chlorbutol), barbiturates, nitrites and narcotics as atropine in big doses.

INTESTINE

Several drugs act mainly by increasing or diminishing the intestinal movements.

THOSE THAT INCREASE THE INTESTINAL MOVEMENTS, act either, simply by expelling the gas, called the **carminatives** or the entire intestinal contents, the **purgatives**.

Even under the normal conditions, a certain amount of gas is formed in the intestine which moves forward with the chyme. In a case of indigestion, a larger amount of it is produced which the normal peristaltic waves may fail to evacuate and this, accumulating, distends the gut. In order to get rid of this distension, the intestinal muscles contract violently and spasmodically, resulting in *colic*.

A similar phenomenon also takes place with drastic purgatives, which cause exaggerated intestinal movements.

Carminatives are drugs, prescribed to help the expulsion of the gas and relieve spasmodic contraction.

These act by relaxing the sphincter and activating the intestinal musculature through the nerves or/and muscles also relieving any irregular painful spasmodic condition (*colic*) in any part of the alimentary tract.

These are volatile oils of all kinds, alcohols, chloroform and ether.

More powerful agents to expel gas especially when intestinal paresis is present are acetylcholine, mecholyl, carbachol, physostigmine, neostigmine and posterior pituitary extract.

Antispasmodics.—These are common adjuvants to cathartics to prevent the griping action often caused by these drugs and also to carminatives to help in their action. These are dilute alcohols, chloroform and ether, cannabis indica, belladonna (also synthetic antispasmodics, p. 616), bromides and the volatile oils as turpentine and camphor. Papaverine, pethidine, nitrites also benzyl benzoate relax muscular spasm.

Purgatives.—The action of these has already been described in detail (see p. 201).

DRUGS THAT LIMIT THE INTESTINAL MOVEMENTS

Excessive intestinal persistalsis has often to be checked as in many cases of diarrhoea. This is done by either diminishing the contraction of the intestinal muscles or their secretions or both.

The intestinal *movements* are markedly lessened by opium and to a less extent by the drugs of the belladonna group, calcium and bismuth salts.

The *secretions* are reduced by all preparations of tannic and gallic acids, salts of lead, silver, zinc, copper, iron, bismuth and aluminium as kaolin and also dilute sulphuric acid. Therefore these are called **intestinal astringents**.

C. Drugs acting on the Gastro-intestinal Contents

1. GASTRO-INTESTINAL ANTISEPTICS.

Drugs are not used for gastro-intestinal disinfection in healthy people as some bacteria must be in the intestinal tract which are helpful in digestion of cellulose. But when putrefactive processes are going on either in the stomach or in the intestines beyond this physiological limit, gastro-intestinal antiseptics are frequently used, although it must be admitted that they are of limited value.

STOMACH

In health, hydrochloric acid present in the stomach is a sufficient antiseptic to stop all bacterial growth but if this is deficient or if from a pathological condition the food is retained too long, bacterial decomposition takes place. To prevent this, dilute hydrochloric acid is given half an hour after food. Other drugs are of less value. These include.—

- (i) Boric, sulphuric or salicylic acids (including salol).
- (ii) Iodine (the weak liquor, in minim doses), phenol and other tar preparations as naphthols and creosote.
- (iii) Essential oils as thymol, menthol and camphor.

INTESTINE

For intestinal disinfection, the drugs selected should not be much soluble, otherwise these may be absorbed too quickly and at the same time should act in alkaline medium in the presence of organic matter, not destroyed by the digestive ferments and should not be very irritant to the alimentary canal.

Recently *sulphonamides* especially sulphaguanidine and succinyl sulphathiozole (p. 365), have been found useful in acute intestinal infections as bacillary dysentery, infantile diarrhoea, ulcerative colitis and to a less extent, in cholera.

Streptomycin is especially useful in tubercular infection: this, *chloromycetin* and *aureomycin* (p. 378, 379) are establishing reputation in different other intestinal infections also.

Napthalene and its less irritating compounds as betanaphthol, benzo-naphthol and bismuth-beta-naphthol (orphenol) were till lately frequently used also guaiacol preparations and salol. Hexyl resorcinol and thymol are occasionally used. Creosote, sodium salicylate and phenol derivatives are likely to be absorbed before these can have sufficient local effects. Insoluble or

partially soluble salts of a few heavy metals are also sometimes used as intestinal antiseptic : these include a few selected salts of mercury, iron and bismuth.

Purgatives (especially the mercurials), by expelling bacteria as well as the nidus for bacterial growth from the intestine, are indirect intestinal antiseptics.

Ferric salts precipitate proteins and the bacteria are carried down with the precipitate though not actually killed and are also indirect intestinal antiseptics.

2. DRUGS USED FOR GASTRO-INTESTINAL DIGESTION.

Pepsin, pancreatin, papain (a powdered vegetable ferment similar in action to pancreatin) and diastase (prepared from germinating grain of barley) are often used. (See p. 20).

Vitamin B complex helps carbohydrate digestion (p. 292).

D. Drugs Acting on the Liver

The liver has varied functions, many of which are not sufficiently affected by any drug to be of much therapeutic value.

1. DRUGS USED FOR BILIARY SECRETIONS.

Drugs believed to increase the secretion of bile are called **cholagogues** but very few of them are really so, and often the phenomenon is rather one of better emptying out of the bile passages and the gall-bladder than actual increased bile formation. Bile in larger quantity appears in the stool in the following way :—

(i) Really *increased secretion*, **choleretics**.—Bile as glycocholic and taurocholic acids, desoxycholic and dehydrocholic acids and their salts given by the mouth or by injection will only do it. Salicylates, histamine, soaps or glucose probably have slight action.

(ii) Bile may be *hurried down* before it finds time to be altered in the intestine. This is done by the so-called cholagogue purgatives as calomel, podophyllum, rhubarb, aloes, cuonymin, iridin, sodium sulphate and phosphate.

(iii) Bile may be *rendered less viscid* which flows out more easily. Salicylates have the best reputation and saline purgatives in general are more or less helpful.

(iv) The natural *hormone* to induce contraction of the gall-bladder and pour out bile is *secretin* formed by the entrance of acid gastric contents into the duodenum. Of the drugs, dilute nitro-hydrochloric acid was believed to be useful but now seldom used. Recently magnesium sulphate 25% solution, olive oil and yolk of an egg introduced into the duodenum, have been found to be more powerful. Histamine also causes increased biliary secretion, but the mode of action is unknown.

OX GALL

Extractum Fellis Bovini (*Ext. Fell. Bov.*), Extract of ox bile.—A dark yellowish green plastic substance with a bitter disagreeable taste prepared from fresh ox bile. Evaporate 1000 ml. of fresh ox bile to $\frac{1}{4}$ th volume, shake with 500 ml. of alcohol (90%). Set aside for the solids to subside: decant the clear solution and filter the remainder: evaporate this in water-bath to firm extract. It contains mucus-free bile salts and the pigments. It is soluble in water and alcohol (90%).

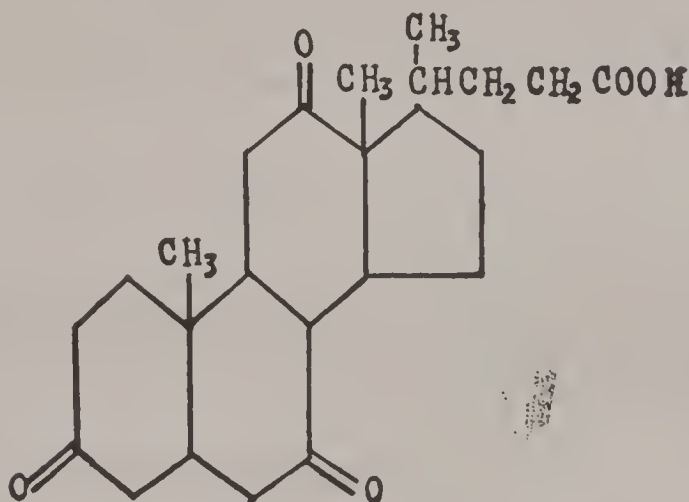
Dose, 5 to 15 grains or 0.3 to 1 gramme.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, Bile has no action.

TAKEN INTERNALLY, by the mouth, bile is **bitter** but it is seldom used as a stomachic in preference to more agreeable vegetable bitters.

Bile contains bile pigments, bile salts, cholesterol, lecithin and some inorganic salts. The pigment is excreted in the urine and faeces. Bile salts are mostly absorbed from the intestine and carried to the liver where by acting on the liver parenchyma they increase the biliary secretion, both its liquid and solid portions, the bile salts being more increased than the pigment. Bile salts are combinations of *taurine* (aminoethyl sulphonic acid) and *glycine* (amino-acetic acid) with cholic acid and related bile acids. These for their specific action on the liver are called **choleretics** as differentiated from **chologogues** which simply hasten the gall-bladder evacuation.



Dehydrocholic acid

(i) By oxidizing cholic acid, *dehydrocholic acid* is formed which is a good choleretic increasing the volume of bile. These bile-salt preparations are therefore used (a) to facilitate **drainage** of the bile duct and is prescribed in cholangitis and cholecystitis: increased bile flow drains out the infected bile. If small stones have formed in the gall-bladder these may also be expelled especially when prescribed with belladonna. But the patency

of the bile passages is essential. (b) In many "liverish" conditions with deficient bile flow these are useful: liver function being stimulated and bile flow increased, the liver functionates better: increased bile flow increases the secretion of pancreas and of intestinal glands. [Usual dose is 0.25 g. available as tablet 3 or 4 times daily and in urgent cases 20% solution parenterally.

(ii) Being alkaline, bile helps the **pancreatic digestion** by neutralising the gastric contents and emulsifying fat. It helps the **absorption of vitamins A, D, E and K** and is particularly indicated in obstructive jaundice showing signs of defective absorption of these vitamins. It also acts as a mild **purgative** by stimulating intestinal peristalsis and often intensifies the action of several drastic purgatives. It is often made into pills with other laxatives.

It is sometimes given as an enema for hard and impacted faecal mass but it is not as satisfactory as oil and soap enema.

(iii) **Circulation velocity** as from arm to tongue is estimated by an intravenous injection of sodium dehydrocholate 3 to 5 c.c. of 20% solution: when bile from the arm vein reaches the tongue, bitter taste is felt in the mouth.

Bile salts preparations however should not be used in bronchial asthma.

Recently it has been found that bile salt inactivates cholinesterase and this probably is responsible for slowing of the heart beat in jaundice through acetylcholine.

The function of cholesterol in bile is not known. It is probably an excretion from the blood. If much increased and the biliary flow is retarded, it may be precipitated to form gall-stone.

Bile is not toxic when given by the mouth. But injected *intravenously*, it causes depression of the heart and central nervous system. On account of the lowering of the surface tension, R.B.C. are hæmolysed. Probably the bile-acids are the toxic elements.

SUMMARY.—Bile helps pancreatic digestion by neutralising gastric acidity and emulsifying fat: it also helps **absorption** of fat-soluble vitamins: it is the only dependable **choleretic** (glycocholate and taurocholate being more often used). Bile with other purgatives is used for constipation.

Non-official and Proprietary Preparations

TAXOL, **PANCROBILIN**, **DESIBYL**, **DESICOL** and **JUBOL** contain bile and are given, 1 to 2 pills, at bed time for constipation.

VERACOLATE contains sodium taurocholate and glycocholate with cascara, phenolphthalein and capsicum in pill, 1 or 2 at bed time.

BICOLATES AND **BILEDASE** are similar preparations and frequently used.

BILRON Pulvules (5 gr.) contain natural conjugated bile acid combined with iron: passes through the stomach unchanged (causing no gastric irritation) and is dissolved in the intestine to act as true cholagogue.

DOSE, 1 to 6 pulvules daily after meals.

SODIUM DEHYDROCHOLATE (*Decholin*) has been thought to be more effective than any other preparation of bile salts favouring an increased

biliary flow and prescribed for many subacute and chronic inflammatory conditions of the bile passages.

Dose, orally 0.25 g. tablets 3 to 4 times daily or 5 to 10 c.c. of 20% solution intravenously.

DEHYDROCHOLIN or CHOLECTRIN in 0.25 g. tablets or in 20% ampoules is also similarly used.

BILAMIDE-CILAG, nicotinyhydroxy methylamide in 0.5 g. tablet orally 2 tablets t.d. for 3 days and one tablet t.d. afterwards and 4% 10 c.c. ampoule intravenously once or twice daily, is used in cholecystitis and cholangitis.

FELAMINE tablets contain 0.3 gm. of a combination of hexamine (0.225 g.) with cholic acid (0.075 g.); 1 to 3 are given 3 times daily for biliary disinfection.

BOLDOA FRAGRANS.—Its tincture (Dose, 10 to 20 min.) and the alkaloid 1 mg. in pill (*Boldine*) are prescribed in hepatic disorders.

2. GLYCOGENIC FUNCTION.

About 1/5th to 1/3rd of total glycogen of the body is stored in the liver amounting to about 300 gm. Glycogenolysis is favoured by adrenaline and thyroxine. Adrenaline is therefore frequently given hypodermically and sometimes intravenously for increasing the quantity of blood sugar when it is suddenly made low by an overdose of insulin. Posterior pituitary extract has the same action.

Glycogenolysis is diminished by the pancreatic extract, toxic metals as arsenic, antimony, phosphorus and also probably by opium, especially by codeine.

Liver is the *great detoxicating agent*. Many toxic substances are broken down in the liver or synthesised (conjugated) into comparatively harmless ones and are excreted by the kidneys. Substances like the heavy metals are partly excreted in the bile: as these cannot be destroyed in the system, these are quickly removed from the blood and temporarily stored in the liver for slow excretion. Accumulation in the liver of such substances as heavy metals and alcohol, chloroform, carbon tetrachloride, ethyl chloride, divinyl ether, avertin, trinitrophenol and cinchophen cause injury to the liver parenchyma.

Several alkaloids as morphine and nicotine are partly destroyed in the liver. Ammonia salts are made into urea. Several of the barbiturates especially evipan are readily split up and this makes them suitable and safe as basal anæsthetic. Camphor, chloral hydrate, avertin and salicylates are paired with glycuronic acid. Sulphonamides are partly acetylated in the liver and are excreted by the kidneys.

In order to lessen the destructive action of many harmful and toxic substances, especially of organic arsenic preparations and chloroform, a good dose of glucose is given before their administration.

The haematinic functions of the liver have already been described (p. 417).

3. NUTRITION IN LIVER DISEASE.

Recent investigations into the etiology, prevention and treatment of progressive liver damage, fatty infiltration and fibrosis showed that in addition to an infection or intoxication, dietetic deficiency plays an important part. A diet containing a plenty of assimilable protein and carbohydrate even with

liberal amount of fat was found of distinct value in early cirrhosis of the liver.

It has further been found that cystine, choline and methionine are essential protective substances. Methionine can serve as a source of choline and cystine and may by itself suffice.

The common property is the possession of a labile methyl group and it is probable that the lipotropic action of methionine is due to its ability to donate such a grouping and to augment the supply of choline when this is deficient.

Vitamin E has also been found to be correlated. (Gyorgy, 1947).

Where a plenty of fish, meat and milk are available and can be assimilated, the supplements of methionine, choline or cystine are not required (Tunbridge, *Practitioner*, 1949): fat need not be severely cut down (Patek, Chalmers and Davidson, *New Eng. J. Med.* 1949).

In addition to methionine, vitamin B complex and crude liver extract in 5 to 10 c.c. doses intramuscularly are used.

MEONINE AND METHIONINE in 0.5 g. tablets, 6 to 12 daily are helpful in acute hepatic disease.

XIV. DRUGS ACTING ON THE URINARY SYSTEM

A. DRUGS INCREASING THE SECRETION OF URINE (Diuretics)

Cushny demonstrated that all diffusible substances in the blood pass through the glomeruli and collect in the tubules in the same concentration as they exist in the blood, nondiffusible or colloidal substances being kept back to maintain nutrition of the tissues. In tubules, a part of this filtrate is re-absorbed especially water and also substances like sugar. These substances are necessary for further use in the body and are called "threshold substances*" and this absorption takes place only upto a certain "threshold limit". That is say, the blood takes these back upto a limit which is more or less constant in the healthy state of the body. Anything in excess is left in the tubules and appears in the urine. On the other hand, urea, uric acid, the urates, phosphates, sulphates, etc., are not necessary and are not, therefore, reabsorbed and these with a certain amount of water left unabsorbed for keeping these in solution, are passed out in the form of urine. The volume of urine may be increased (diuresis, G. *dia*, through and *ouron*, urine) in the following way.

* Sugar, chlorides, creatine and bicarbonates have high threshold value : so also water. K, Cl, Ca ions are partially reabsorbed (semi-threshold). Urea and uric acid may be absorbed in minute quantity and sulphate and creatinine are never absorbed (nonthreshold).

- (i) By increasing the blood flow through the glomeruli.
- (ii) By increasing the fluid volume of blood.
- (iii) By increasing the filtrate concentration of blood.
- (iv) By increasing the fluid flow through the renal tubules.
- (v) Miscellaneous diuretics.

These are detailed as follows.

(1) Greater the quantity of blood passing through the kidneys in a given time, the more is the secretion. This method of augmenting secretion of urine by increasing the glomerular blood flow is called "**circulation diuresis**". *Digitalis*, *strophanthus*, *squill*, *adrenaline*, *caffeine*, *alcohols*, *spirit of nitrous ether* and *cold applicatcn* to the skin act in this way.

(2) The richness of the blood colloids.—Greater the concentration of protein in the blood, more water it can retain and a less amount tends to pass out of it through the glomeruli and consequently less is the secretion of the urine. If, on the other hand, the blood is diluted as by a copious *drink* of *water*, or an *injection of normal saline* solution, the blood colloids can no longer retain so much fluid and in order to regain the balance, the surplus fluid passes out through the glomeruli causing an increased secretion of urine: "**Colloid dilution diuresis**".

(3) The concentration of the filtrate.—The crystalliods as: *chlorides*, *carbonates*, *acetates*, *citrate*s, *nitrate*s, *iodide*s, *bromide*s: to a less extent, *tartrate*s, *phosphate*s and *sulphate*s of alkaline metals (potassium, sodium or lithium) also of *ammonium*, *sugars* and *urea*, if taken by the mouth and absorbed into the blood, increase the concentration of blood crystalloids which by raising the osmotic tension, abstract water from the tissues. This produces a relative hydræmia, disturbing the colloid balance. An increased quantity of water containing these substances passes out of the glomeruli and collects in the tubules. As these are mostly non-threshold substances, they are not much reabsorbed: consequently water keeping these in solution in quantity sufficient to make an isotonic fluid, is retained in the tubules, increases the local pressure and produces diuresis by salt action. This method of increased urination may be called "**salt action diuresis**".

Given by the mouth, the acetates have a better taste and act best. The next in order of preference are the citrates, nitrates, chlorides, carbonates and the bicarbonates. The tartrates are feebly absorbed. The phosphate and the sulphates are even less so. The tartrates are feeble diuretics and phosphates and sulphates are still weaker. The last three act mainly as purgatives. So to have sufficient diuretic action, the salt (i) should be easily absorbable from oral administration and (ii) it should have no disadvantageous specific action of the negative ion; thus although a bromide or an iodide should be a diuretic, none of them can be used for this purpose. Of the positive ions, potassium salts are more diffusible, have

a lower threshold than sodium salts and so are more powerful diuretics.

Ammonia salts (forming urea), urea, glucose and sucrose are also powerful diuretics.

Certain *acid forming salts* as calcium chloride (p. 271) and ammonium chloride also act in nearly the same way. These by causing acidosis lessen salt adsorption by tissue protein; salts made free in this way increase non-colloidal constituents of blood plasma causing diuresis.

Thyroxine causes diuresis by mobilising sodium chloride and water in the beginning and afterwards from an excess of urea obtained from improved tissue metabolism (p. 407).

(4) The faster the fluid passes through the renal tubules, the less is the time for reabsorption. Drugs having the action of increasing this rate of tubal flow may be called "**specific diuretics**".

These are *volatile oils* (especially oils of buchu, juniper, copaiba and sandal wood oil), *caffeine-theobromine-theophylline group*, *uva ursi*, *mercurial* diuretics and *cantharidin* (in minute doses). As these act by causing a certain amount of irritation to the tubular epithelium, these should not be prescribed in any acute stage of the kidney diseases.

Thus it will be seen that the first two groups have their action mainly on the glomeruli and are called "**glomerular**" and the last two, for the same reason, "**tubular diuretics**".

CHOICE OF DIURETICS

(i) Œdema with cardiac decompensation.—*Digitalis*, *mercurials* with acidifying agents, urea and xanthines.

(ii) Ascites with portal stasis.—*Mercurials* with acidifying agents, *theophylline* and urea.

(iii) Acute glomerulonephritis.—*Saline* diuretics and hypertonic glucose solution intravenously.

(iv) Subacute glomerulonephritis.—*Salines*, hypertonic glucose, xanthines and volatile oils as buchu.

(v) Œdema with nephrosis.—In addition to those in (iv), thyroid extract, urea and occasionally *mercurials*.

LIQUOR AMMONII ACETATIS FORTIS

(*Liq. Ammon. Acet. Fort.*)

The strong solution of ammonium acetate is prepared by the intraction of glacial acetic acid 453 g., ammonium bicarbonate 470 g., strong solution of ammonia 100 ml. or q.s. and distilled water to make 1000 ml. It is a thin syrupy liquid with the smell of ammonia and acetic acid. Contains 57.5% w/v of C₂H₃O₂N.

Dose, 15 to 60 minims or 1 to 4 ml.

OFFICIAL PREPARATION.—*Liquor Ammonii Acetatis Dilutus* (*Liq. Ammon. Acet. Dil.*), See p. 49. Dose, $\frac{1}{2}$ to 1 fl. oz. or 8 to 30 ml.

Pharmacology [and Therapeutics]

Ammonium acetate is an indifferent salt and has no external action. Taken internally, like the corresponding alkaline salts it is readily absorbed, oxidised in the tissues and finally changed into urea and excreted. It is a popular **diaphoretic** [and frequently prescribed in mild catarrhal fevers] and a **diuretic**. The action is mainly due to urea formation. It is specially suitable in acute inflammatory condition in the genito-urinary passages, as in gonorrhœa, *B. coli* infection or acute nephritis].

LIQUOR AMMONII CITRATIS DILUTUS (Not official), in $\frac{1}{4}$ to 1 fl. oz. doses is occasionally prescribed for the same purpose.

UREA, Carbamide, $\text{CO}(\text{NH}_2)_2$

Urea is the diamide of carbonic acid, prepared from ammonium cyanate. Colourless, nearly inodorous, transparent prismatic crystals with cooling saline taste. Soluble in 1 of water and in 5 of alcohol (90%).

Dose, 75 to 225 grains or 5 to 15 grammes.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY.—Urea has no specific local action when applied on the skin or taken by the mouth. But applied on a septic wound such as carbuncle or cellulitis in saturated solution or as crystals, it acts as a **lymphagogue** with **slight analgesia**: in about 2 days the **sloughs are separated** forming a clean base, the result being more rapid than of magnesium sulphate paste. Urea with sulphanilamide 10% of each in a water soluble base is an excellent application: urea may also be used with penicillin.

TAKEN INTERNALLY.—Urea is rapidly absorbed from the intestine and excreted promptly and completely into the renal tubules. As it is not much reabsorbed (of low threshold value), it is eliminated along with water keeping it in solution causing **profuse diuresis**. A small part of it is excreted in the sweat also. Its excretion is impaired in chronic nephritis but not in subacute glomerulo-nephritis or nephrosis. It is therefore indicated as diuretic in the last two conditions only.

[Urea in 15 to 20 gm. dose daily is sometimes given as diuretic in general anasarca of subacute nephritis and nephrosis and less commonly of congestive heart failure, with benefit. In chronic nephritis, the capacity of the kidneys to concentrate urea in the urine is the measure of their functional efficiency. Fifteen grammes of urea dissolved in 100 c.c. of water is given in the morning on empty stomach. Urine is collected one hour and two hours after. If the kidneys are functionally efficient, and no excessive diuresis has taken place, the first sample must contain at least 1.5% and the second sample, 2% of urea. If less, it shows kidney insufficiency, *McLean's test*.]

Urea appears to potentiate the antibacterial action of the sulphonamides. Urea orally 30 grm. with 2 grm. of sulphadiazine every 4 hours has been found to have much more intensive effect. (Londe and Gardner, *J.A.M.A.*, 1948.).

SUMMARY.—Urea is a suitable local application on a sloughing wound (more active with sulphanilamide or penicillin): it is a non-toxic diuretic in subacute nephritis and nephrosis and rate of its elimination in chronic nephritis is the test of kidney efficiency. It seems to potentiate antibacterial action of sulphonamides.

Important urea products are *barbiturates*, *carbromalum* and *bromural* also *quinine urea* and *urea stibamine*.

SOME VEGETABLE DIURETICS (Not official)

UVÆ URSI FOLIA.—This contains two glucosides the more important of which is *arbutin*; also a large quantity of *tannin*. Given by the mouth, arbutin is partly excreted unchanged and partly changed into hydroquinone which gives a greenish brown colour to the urine. These in the process of excretion, acts as *diuretic* and also to some extent, *astringent* and *antiseptic*⁴⁸⁵ to the urinary passages. The infusion was given for many infective conditions in the kidneys and the bladder but now nearly obsolete.

In large doses it is a *gastro-intestinal irritant* causing nausea, vomiting and diarrhoea. The crude preparation is more irritant than the glucoside. Dose of infusion, $\frac{1}{2}$ to 1 fl. oz. (prepared with 1 in 20 of boiling water).

SCOPARII CACUMINA (Broom tops). It contains a resinous substance, *scoparin* and an alkaloid, *sparteine*. The *diuretic action*⁴⁸⁷ is probably due to the former. For this purpose, the infusion is often prescribed. Sparteine was formerly believed to be acting like digitalis on the heart but this view has not been confirmed. It slightly slows the heart by direct *depression of the heart muscles* and therefore does not increase the output. It is slightly *cerebral sedative*, but spinal cord excitant, causing tetanic spasm in toxic doses. The nerve-endings, both motor and sensory, are paralysed and the phrenic is first affected.

It paralyses the sympathetic ganglia also. The action in some respects thus resembles coniine and gelseminine. It is not now-a-days much prescribed.

AGROPYRUM (Couch grass).—It is *demulcent* and slightly *diuretic*⁴⁸⁸ and the decoction is sometimes used for this purpose.

A decoction of **MORINGA PTERYGOSPERMA** (*Sajina*) root bark; **ASPARAGUS RACEMOSUS** (*Satamuli*) leaves and roots or **BOMBAX MALABARICUM** (*Simul*) young fruits and gum, is given for scanty urination with stranguary and also for subacute dysentery.

BÆRHAAVIA RIPENS (*Punarnava*) and **TRIANTHEMA PORTULACASTRUM** (*White Punarnava*): **IND. PHARM. LIST.**—These are well-reputed diuretics of Ayurveda. The plant grows abundantly all over India as a creeping weed and the white variety is preferred. It contains an alkaloid and a large amount of potassium nitrate both of which are *diuretics*. The alkaloid given intravenously, causes a marked rise in blood pressure and

- | | |
|-----------------------------|---------------------------------|
| (486) R | Inf. Digit. Rec. min. 120 |
| Hexamin. gr. $7\frac{1}{2}$ | Inf. Scopar. Rec. ad. fl. oz. 1 |
| Ol. Santal. | For cardiac dropsy. |
| Ol. Copaib. aa. min. 10 | (488) R |
| Alcohol (90%) min. 60 | Pot. Cit. |
| Inf. Uvæ Ursi ad. fl. oz. 1 | Sod. Bicarb. aa. gr. 20 |
| (487) R | Syr. Aurant. min. 60 |
| Pot. Acet. gr. 20 | Decoc. Agropyri ad. fl. oz. 1 |
| Liq. Ammon. Acet. Dil. | For subacute nephritis. |
| min. 60 | |

free diuresis. The fresh juice, decoction or the extract of the plant is frequently prescribed with other diuretics for general anasarca with scanty secretion of urine^{489, 490}. Its Sanskrit name, *shothaghni* or dropsy-curer testifies its reputation as a diuretic. It is *laxative* also and in big doses, act as purgative.

TRIBULUS TERESTRIS (*Gokshura*).—It contains an alkaloid, an essential oil and nitrates. The decoction of the fruits is a good *diuretic*.

B. DRUG DECREASING THE QUANTITY OF URINE (Antidiuretic)

The only drug of importance is the hormone of the *posterior pituitary gland*. Marshall (1934) showed that reabsorption of water up to maximum limit is done by the cells of the loop of Henle; the antidiuretic hormone activates these cells. Five to 10 units of the hormone available as *Pitressin* hypodermically morning and evening usually controls polyuria of diabetes insipidus. (See p. 403).

C. DRUGS ALTERING THE REACTION OF THE URINE

(i) Making the Alkaline Urine Acid

The most important of these is *Acid sodium phosphate*, the natural acid salt of the urine. Big doses of *calcium chloride* and *ammonium chloride* also do the same by combining with sodium carbonate in the blood and liberating hydrochloric acid. *Mandelic acid* preparations are even more powerful. Less active are *benzoic acid* and the benzoates. These are excreted as hippuric acid which makes the urine acid. The *salicylates* (excreted as salicyluric acid) and *boric acid* also make the urine slightly acid.

The urine is made alkaline by bacterial decomposition and as most of the bacteria are killed in the acid medium, these drugs, by making the urine adequately acid, are helpful **urinary antiseptics**.

SODII PHOSPHAS ACIDUS (*Sod. Phosph. Acid.*), Sodium dihydrogen phosphate, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$

Prepared by the interaction of sodium phosphate and phosphoric acid. It contains not less than 98% of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$. Colourless crystals or crystalline powder, with acid saline taste: soluble in 1 of water making an acid solution.

Dose, 30 to 60 grains or 2 to 4 grammes.

(489) B

Pot. Cit. gr. 15
Tinct. Digit. min. 10
Ext. Punarnava Liq. min. 60
Syr. Aurant. min. 60
Inf. Scapar. ad. fl. oz. 1
For cardiac dropsy.

(490) B

Pot. Acet. gr. 15
Liq. Ammon. Acet. Dil.
min. 120
Ext. Punarnava Liq. min. 60
Syr. Limon. min. 60
Inf. Scapar. ad. fl. oz. 1
For subacute nephritis.

Pharmacology [and Therapeutics]

The normal urine is acid in reaction on account of its containing acid sodium phosphate. This normal reaction changes by taking alkalis in big doses which form alkaline sodium phosphate (Na_3PO_4) but this happens much more commonly from bacterial decomposition of the urine, so that urea of the urine is broken down into ammonia and this combining with acid sodium phosphate, forms alkaline triple phosphates, often seen in such urine as a flocculent deposit.

Acid Sodium Phosphate, [30 grains, 3 or 4 times daily], given by the mouth in such cases, restores the normal acidity of the urine and as in an acid medium bacteria mostly die, acid sodium phosphate is one of the dependable **urinary antiseptics** [and is often *alternated* with hexamine, the latter acting best in the acid medium so produced]. Its action is slow as it is not readily absorbed. Given in big doses, it may cause diarrhoea by local salt action on the intestine. Its administration should then be temporarily stopped.

It is sometimes useful in **oxaluria** owing to its solvent action on calcium oxalate. [About 1 oz. in 100 fluid oz. of distilled water should be given daily by the mouth].

SODIUM HEXAMETAPHOSPHATE (Not official), 5% is used as a *dusting powder* in excessive perspiration and in certain skin eruptions and is a prophylactic against mycotic infection of the toes. It is also used to *prevent precipitation of calcium* compounds and is used in pharmaceutical preparations of external use. It is sometimes also added to water for boiling surgical instruments (prevents rusting).

AMMONII CHLORIDUM (*Ammon. Chlorid.*),
Sal Ammonia, NH_4Cl , *Nishadal*

Ammonium chloride is prepared by neutralising ammonia with hydrochloric acid and purifying the product. It should contain not less than 99.5% of NH_4Cl , dried in vacuo over sulphuric acid.

A white, inodorous slightly hygroscopic crystalline, granular powder with saline cooling taste: soluble in 3 of water and in 60 of alcohol (90%). **DOSE**, 5 to 60 grains or 0.3 to 4 gramme.

Pharmacology [and Therapeutics]

APPLIED LOCALLY, Ammonium chloride in solution has a cooling effect and is used along with alcohol (*Lotio Evaporans*, p. 446) for sprains and bruises. The vapour inhaled tends to increase the secretion of the mucous membranes. [Lozenges each containing 2 to 3 grains are often sucked for sore throat and freshly prepared ammonium chloride vapour in spray of 1% solution is used for nasal and pharyngeal catarrh].

Ammonium chloride is absorbed much more rapidly from the stomach and the intestine than either potassium or sodium chloride. If given in a concentrated solution, the gastric mucous membrane is so irritated that it may cause vomiting.

In the liver ammonia-ion is changed into urea, and chlorine into hydrochloric acid : the latter immediately combines with sodium or potassium in the blood. It is excreted as sodium or potassium chloride and thus reduces the plasma alkalies and the urine tends to become more acid. Acidosis lessens adsorption of salts by proteins : the free salts in the blood cause diuresis. Urea liberated also helps. This is specially profuse if administered with a mercurial diuretic.



In big doses, (120 grains daily), it is used frequently in hepatic ascites alternating with injection of mersalyl. Profuse diuresis often follows evacuating the fluid collected. For alkalosis a 0.8% solution is sometimes given very slowly intravenously but oral administration is often sufficient.

It is of value in chronic lead poisoning, given in 15 to 30 grains doses daily : it causes some acidosis which hastens elimination of lead through the urine (See p. 273).

From its local salt action, it is a feeble cholagogue, and in the same way a diaphoretic and is also frequently used in cough mixtures as an expectorant especially if the sputum is stiff and tenacious but its taste is nasty.

SUMMARY.—Ammonium chloride is anticatarrhal on the upper respiratory tract : mild diaphoretic, expectorant and feeble cholagogue ; it reduces the plasma alkalies acting as a diuretic (with mercurial diuretics and in chronic lead poisoning).

ACIDUM MANDELICUM, $\text{C}_6\text{H}_5\text{O}_3$

This is *Phenylglycollic acid*, $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CO}_2\text{H}$, prepared by the action of cyanide on sodium bisulphate, addition of compound of benzaldehyde and hydrolysis of mandelonitrile thus produced. It contains not less than 99.5% of $\text{C}_6\text{H}_5\text{O}_3$.

White crystals but slowly become yellow when exposed to light : almost inodorous with acid saline taste : soluble in about 7 parts of water and 1 part of alcohol (90%).

Dose, 30 to 60 grains or 2 to 4 grammes

CALCI MANDELAS (*Calc. Mandel.*), Calcium Mandelate ($\text{C}_6\text{H}_5\text{CHOH}.\text{CO}_2)_2\text{Ca}$.

Calcium mandelate is prepared by double decomposition between sodium mandelate and a calcium salt : contains not less than 99% of $\text{C}_{16}\text{H}_{14}\text{O}_6\text{Ca}$.

A white micro-crystalline powder with slightly aromatic smell and saline taste. Very slightly soluble in water and insoluble in alcohol 90%.

Dose, 30 to 60 grains or 2 to 4 grammes.

CHOHCO_2H



Pharmacology [and Therapeutics]

Ketogenic diet producing β -hydroxybutyric acid has been found to be an efficient urinary disinfectant for its acid properties (Fuller, 1933) but for therapeutic purpose such a diet is not suitable. *Mandelic Acid* (α -hydroxy α -toluic acid) has

later on been found to be quite as effective in rendering the urine highly acid in a short time (Rosenheim 1935). As it irritates the stomach, it is prescribed in 3 gm. doses neutralized by 1·6 gm. of sodium bicarbonate or as *Sodium Mandelate* 3·5 gm. 4 times daily. In order to help acidification, 1 to 2 gm. of ammonium chloride is also given one hour previously. More recently, *Ammonium Mandelate* is given. As it is very hygroscopic, an elixir of it is prescribed. Sometimes nausea, vomiting and even diarrhoea may follow. *Calcium mandelate* is often better tolerated and more agreeable: simultaneous administration of ammonium chloride is not necessary. These should not be given if gross renal deficiency is present. These fail if the infection is by ammonia forming bacteria as *B. pyocyaneus*. [The mandelates have been found effective in urinary infections especially by *B. Coli* and does not cause much toxic symptoms. Bactericidal effect is apparent in 3 days and the total course is for 7 to 10 days. In case of relapse, another course may be given].

By restriction of fluid intake to about 40 oz. daily, pH of urine is kept between 5·2 to 5·5. As this may cause renal irritation, occasionally hæmaturia, the administration should not be continued for more than 10 days at a time.

Recently sulphonamides and antibiotics (p. 382) are giving so satisfactory results that most of other types of chemical antiseptics are getting into the back-ground. Mandelic acid preparations may have a field if the infection is sulpha and antibiotic resistant.

TOXIC SYMPTOMS are nausea, vomiting, giddiness, buzzing noise in the ears and occasionally, urticaria.

COMMERCIAL PRODUCTS of ammonium mandelate are *Ammoket* and *Uromaline*. *Mandecal*, calcium mandelate (75%) pleasantly flavoured: dose, one level dessert-spoonful 4 times daily. *Mandelamine* (methenamine mandelate), 3 tablets of 4 gr. (0·25 g.) each after meals and on retiring at night, claimed to be effective in sulpha and streptomycin resistant cases and is non-toxic.

(ii) Making the Hyperacid Urine Alkaline

The drugs are the carbonates and bicarbonates of potassium and sodium also acetates, citrates and tartrates, as these are oxidised into carbonates. The chemical reaction that takes place has already been explained: acid sodium phosphate (the normal acid of the urine) is changed into alkaline sodium phosphate (p. 250). Sodium lactate (p. 255) is also used.

These are useful in acute inflammatory conditions of the urinary passages, relieving strangury and increasing the quantity of urine by salt action. In some cases, hyperacidity of the urine is associated with the formation of gravels (urate or oxalate). In such conditions, these alkalis by causing diuresis are helpful in flushing out the kidneys and hence are called **lithontriptics**.

D. URINARY ANTISEPTICS

The bacteria grow best in the urine when the latter is nearly neutral or feebly alkaline. Both hyperacid and hyperalkaline urine (between the range of pH 4.5 to pH. 10) inhibit them. The normal urine is sterile: this is due to its acid reaction, (pH 6.4 to 6.8). The physiological urinary antiseptics are therefore drugs that make the urine acid. These are *acid sodium phosphate*, *ammonium chloride*, *calcium chloride*, *boric acid*, *benzoates*, *salicylates* and best of all, the *mandelates*. Of all these, the last only can lower the pH to 5.2 with safety.

Those that make the urine hyperalkaline are *bicarbonates*, *acetates* and *citrates* of sodium and potassium given in 60 to 90 grains doses every four hours. [In *B. Coli* infection, the urine is fairly acid and the organisms are somewhat inhibited by making it alkaline or making rapid changes from acid to alkaline and from alkaline to acid again].

Most of the other urinary antiseptics are of limited value on account of their brief contact. In fact any urinary antiseptic either given internally or introduced locally has many limitations.

Hexamine is excreted in the urine. It is decomposed in the acid medium to evolve formaldehyde which is an antiseptic. But given in big doses, to cause sufficient concentration of the antiseptic in the urinary passages, it may cause vesical irritability, even hæmaturia. *Hexyl resorcinol* is equally active both in acid and alkaline urine but is a feeble antiseptic.

In most cases, in order to ensure a sufficient concentration of the antiseptic in the urine a large quantity of fluid and diuretic drugs are avoided during their administration.

Volatile oils as oils of juniper, copaiba, cubebs, sandal wood oil, buchu and also uva ursi are of some help in chronic infective conditions of the urinary passages, especially in gonorrhœa. Oil of turpentine is too irritant to be used. *Boric acid*, *benzoates* and *salicylates* are mild antiseptics and are also sometimes used.

Mandelates are more effective but the urine must be sufficiently acidified and big doses cause gastro-intestinal irritation.

Pyridine compounds as neotropin, and the *acridine dyes* as euflavine and methylene blue are also useful in some cases.

But these have been now largely replaced by newer and safer disinfectants.

(i) *Sulphonamides* have been found to cause much more dependable urinary disinfection than any other chemical preparation so far known (p. 366).

Sulphonamides are admissible in acute infections provided no gross renal deficiency is present: act in alkaline urine (urine has therefore to be alkalisied), fairly nontoxic and cheap.

(ii) *Antibiotics* have specific action on the urinary bacteria (see p. 381).

It will thus appear that *sulphonamides* are effective in *B. Coli*, gonococcic, streptococcic, staphylococcic and to some extent in *proteus vulgaris* and pyocyanous infection. *Penicillin* is specially useful in gonococcic, streptococcic and staphylococcic infections. *Streptomycin* is useful in *B. Coli*, *proteus vulgaris*, and to some extent in pyocyanous, streptococcal, staphylococcal and in tubercular infections.

Chloromycetin and *Aureomycin* (p. 378) are also useful in certain cases especially in those resisting other treatments.

HEXAMINA, Urotropine, Methenamina, Hexamethylene-tetramine, $C_6H_{12}N_4$ (Not official)

Colourless crystals or white powder without any smell and freely soluble in water. Prepared by the interaction of formaldehyde and ammonia.

Soluble in $1\frac{1}{2}$ of water with an alkaline reaction. A solution for injection is sterilised by filtration. Boiling decomposes hexamine.

Dose, 10 to 30 grains or 0.6 to 2 grammes. Available as tablets also.

Pharmacology [and Therapeutics]

APPLIED EXTERNALLY, it has no action. But TAKEN BY THE MOUTH, it is slightly decomposed in the stomach but mostly absorbed and this is so quick that it appears in the urine in less than one hour. In acid urine, it liberates formaldehyde which acts as an antiseptic.



[It is therefore useful in cystitis and septic condition of the bladder]. If the urine is alkaline, acid sodium phosphate or ammonium chloride is given beforehand to make it acid. [Ten grains of hexamine should be alternated with 30 grs. of acid sodium phosphate, 2 or 3 times a day]. The disadvantage is that a high acidity (*pH* at least 6), necessary for its optimum action, cannot be maintained long without causing disagreeable symptoms of irritation. Further, the liberated formaldehyde, if in excess, causes irritability of the bladder and even hæmaturia especially so in a susceptible person. If a large quantity of water is also taken the antiseptic action is lessened as formaldehyde is thereby diluted. The benefit following its administration is consequently not equally marked in every case. For these reasons, hexamine is being replaced by several newer urinary antiseptics.

It diffuses readily and is found in all secretions of the body as bile, pancreatic secretions, cerebro-spinal fluid, bronchial and nasal secretions. For inflammatory conditions in these places also, hexamine is occasionally used especially for various forms of **cholangitis**.

[Hexamine is given in 10 grs. doses increased to 30 grs. mixed with sodium salicylate and big doses of alkalies, 3 to

4 times daily¹⁹¹. Sodium salicylate drains the bile passages and alkalies keep the urine alkaline, so that not much formaldehyde is liberated in the urinary passages. If this is not done, severe vesical irritability may result from such big doses of hexamine. The actual mode of action in cholangitis is difficult to say but there are clinical evidences in its favour].

It is sometimes given in the 3rd to 4th week of typhoid fever to prevent typhoid cholecystitis and bacilluria¹⁹².

Hexamine is also given intravenously in 40% solution in 2 to 5 c.c. doses, 2 to 3 times a week for more intensive action on the bile passages often combined with sodium salicylate.

COMMERCIAL PREPARATIONS

AMPHOTROPIN (Hexamine camphorate), HELMITOL (Methyleitrate of hexamine), 1 to 2 tablets, 3 times daily : urinary antisepsics.

CYLOTROPIN in 5 c.c. ampoules each containing 30 grs. of hexamine, 12 grs. of sod. salicylate and 3 grs. of caffeine sod. salicylate, is given intravenously or intramuscularly for biliary and urinary disinfection.

URODONAL (Hexamine with a small amount of sidonal and lysidine) is a granular effervescent preparation given in tea-spoonful doses, 2 to 3 times daily, for uric acid diathesis.

XV. DRUGS ACTING ON THE UTERUS

Drugs are mainly used to increase the strength of the uterine contractions and sometimes to relax them also. Those that increase the activity of pregnant uterus are called *ectolics* and those that do the same to a non-pregnant one, increasing the menstrual flow, are called *emmenagogues*.

Uterine Excitants

The drugs act directly on the uterine muscles, on the extrinsic nerves or on the pelvic circulation. Uterus is supplied by the autonomic nerves through the hypogastric nerves (having both sympathetic and parasympathetic fibres : see fig. 37) which carry both excitatory and inhibitory impulses. So the drugs that act on these, may act in either way, according to the relative activities of the two nerve sets.

(i) *Drugs acting directly on the muscles.*—Estrone, Posterior pituitary extract, Quinine, Histamine, Lead, Veratrine and Barium.

(ii) *Drugs acting on the nerve-endings.*—Ergotoxine, Ergotamine, Ergometrine, Adrenaline, Tyramine, Pilocarpine, Physostigmine ; also probably cotton root bark.

(491) R

Sod. Salicyl. gr. 10 to 15
Sod. Bicarb. gr. 20 to 60
Hexamin. gr. 10 to 30
Syrupus min. 60
Aq. ad. fl. oz. 1

For subacute cholangitis.

(492) R

(1) Acid. Sod. Phosph. gr. 30
Syr. Aurant. min. 60
Aq. Chlorof. fl. oz. 1
(2) Hexamin. gr. 10
Aq. Chlorof fl oz. 1
To be taken alternately, t.d.

(iii) *Drugs acting on the sympathetic ganglia.*—Hydrastine and Coniine.

(iv) *Drugs acting on the lumbar centre.*—Strychnine and Picrotoxin.

(v) *Drugs acting on the pelvic circulation or reflexly.*—Aloes, drastic purgatives; applications of hot bath, hot vaginal douche; irritants as cantharidin, volatile oils as turpentine, savin and thyme.

Uterine Sedatives

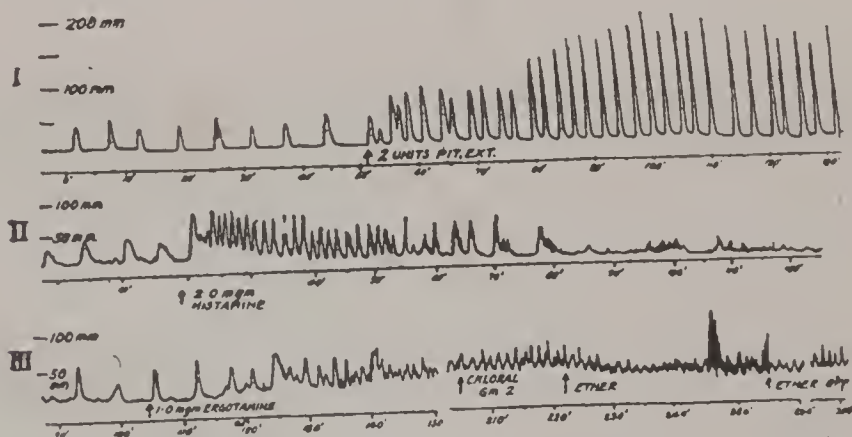
These represent less defined group and are less effective.

Progesterone is the physiological uterine sedative. General *anæsthetics* as chloroform; central *sedatives* as morphine, *cannabis indica*, chloral hydrate or bromides and drugs of the *belladonna group* are sometimes given to diminish the uterine contractions in threatened abortion and in menorrhagia. But in therapeutic doses, they do not very much interfere with normal uterine contractions.

Viburnum is of doubtful value.

Of the morphine group, probably *papaverine* is more effective. *Progest-erone* is the real inhibitor of *œstrin* (the activator of uterine contractions) and is useful as preventive in repeated abortions and administered along with vitamin E. (See p. 287, 395).

Emmenagogues.—*Ecbolics* in smaller doses increase the menstrual flow. Sometimes its deficiency is due to ovarian hypofunction and anæmia requiring ovarian hormone (*œstrone*), iron, vitamins B complex and C also arsenic and strychnine.



(Bourne and Burn from Clark)

Fig. 59.—The action of drugs on human uterus. (I) The effect of 2 units of *posterior pituitary extract*: immediate and prolonged response in the form of increased contractions. (II) The effect of 2 mg. *histamine* hypodermically: immediate increased contractions, soon followed by decrease in uterine activity. (III) The effect of 1 mg. *ergotamine* hypodermically: delayed but prolonged action with uterine spasm.

Uterine Haemostatics.—In addition to drugs increasing the uterine contraction as ergot, posterior pituitary extract or adrenaline, hydrastine and cotarnine are of some value.

ERGOTA (*Ergot*), *Ergot*, *Secale cornutum*

Ergot is the mycelium (sclerotium) of *Claviceps purpurea* that grows in the ovary of common rye (*Secale Cereale*). As the ergot develops, the rye grain completely disappears.

Subcylindrical, slightly curved and tapering towards the ends : 1 to 4 cm. \times 2 to 7 mm., longitudinally furrowed on each side, obscurely 3 or 4 sided. Straight or arcuate : dark violet-black externally, whitish or pinkish-white within. The odour and taste are characteristic. It should contain not less than 0.2% of the total alkaloids of *Ergot*, calculated as ergotoxine : of this not less than 15% is water soluble alkaloids calculated as ergometrine.

The chief constituents are (i) *Ergotoxine* ($C_{33}H_{33}O_5N_5$) and *Ergotamine* ($C_{33}H_{33}O_5N_5$) also *Ergosine* ($C_{30}H_{31}O_5N_4$) and *Ergocristine* ($C_{35}H_{35}O_5N_5$) which are amorphous alkaloids insoluble in water but soluble in alcohol. (ii) *Ergometrine* ($C_{19}H_{23}O_2N_3$), a crystallisable alkaloid, soluble in water. (iii) *Ergotinine*, physiologically inactive. (iv) *Tyramine* ($C_8H_{11}ON$). (v) *Histamine* ($C_5H_9N_3$) or *Ergamine* : the last two are protein decomposition products : also acetyl choline, ergosterol, a fixed oil, carbohydrates, tannin and trimethylamine giving the peculiar smell.

OFFICIAL PREPARATIONS.—(i) *Ergota Præparata* (*Ergot. Præp.*), This is powdered ergot, from which fat has been removed. It should contain 0.2% of the total alkaloids of ergot calculated as ergotoxine : of this not less than 15% should be water soluble alkaloid, ergometrine : 8 grains contain 1/60 gr. of total alkaloids and 1/400 gr. of water soluble alkaloids. Prepared ergot should be kept in an airtight container. Dose, 2½ to 8 grains or 0.15 to 0.5 gramme. (ii) *Tabellæ Ergotæ Præparatæ* (*Tab. Ergot. Præp.*), See p. 57. Dose as of *Ergotæ præparata* : each tablet contains 2½ grains. (iii) *Extractum Ergotæ Liquidum* (*Ext. Ergot. Liq.*), See p. 39. It should contain 0.06% of the total alkaloids, calculated as ergotoxine when freshly prepared ; after storage, not less than 0.04%. Dose, 10 to 20 minims or 0.6 to 1.2 ml.

ERGOTOXINÆ ÆTHANOSULPHONAS, Ergotoxine Ethanosulphonate : Ergotoxine. (Not official)

Dose, 1/120 to 1/60 grain or 0.5 to 1 mg. by subcutaneous or intramuscular injection.

ERGOMETRINÆ MALEAS (*Ergometrin. Maleas*), Ergonovine Maleate, $C_{19}H_{23}O_2N_3$, $C_4H_4O_4$.

Ergometrine Maleate is acid maleate of ergometrine, obtained from ergot : contains not less than 95% of $C_{19}H_{23}O_2N_3$, $C_4H_4O_4$ of the substance dried in vacuo at 110°.

A white or faintly yellow inodorous microcrystalline powder soluble at 25° in about 36 of water, 100 of alcohol 90% but insoluble in solvent ether and in chloroform.

Dose, orally, 1/120 to 1/60 grain or 0.5 to 1 mg. By intramuscular injection, 1/240 to 1/120 grain or 0.25 to 0.5 mg. By intravenous injection, 1/480 to 1/240 gr. or 0.125 to 0.25 mg.

Injectio Ergometrinæ Maleatis (*Inj. Ergomat. Maleat.*), See p. 43. Strength of ergometrine maleate is 85 to 110% of the amount stated in the label. The solution is put in ampoules, air replaced by nitrogen, sealed and sterilised by autoclaving.

Dose is of Ergometrine Maleate.

If the strength is not stated, one containing 1/120 gr. in 15 min. or 0.5 mg. per ml. is dispensed.

ERGOTAMINÆ TARTRAS (*Ergotam. Tart.*), Ergotamine Tartrate, $(C_{33}H_{35}O_5N_5)_2C_4H_6O_6$.

Ergotamine Tartrate is the tartrate of an alkaloid obtained from ergot.

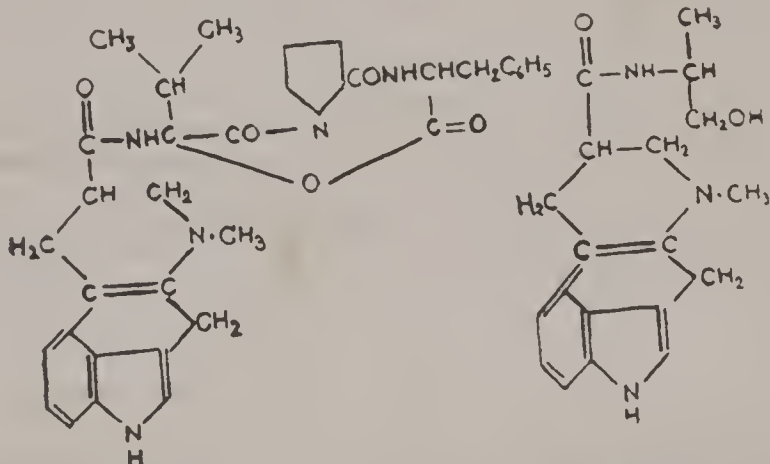
Colourless crystals or crystalline powder, readily soluble in water often making a cloudy solution which clarifies on adding tartaric acid. Soluble in 500 parts of alcohol (90%).

Dose, 1/60 to 1/30 grain or 1 to 2 mg., as *single dose orally*. 1/240 to 1/120 gr. or 0.25 to 0.5 mg. by *subcutaneous injection*.

Pharmacology [and Therapeutics]

Contamination of an edible grain by a poisonous fungus was known even in 600 B.C. In 1582 Lonicer found that this was causing pain in the womb. The first physician to use this was Desgranges and soon after Stearns (1807) introduced this for "quickening" child-birth. It was introduced in Europe later on.

Tanret first isolated an alkaloid which is now known as *ergotinine* (1875) but inert. *Ergotoxine* was found by Barger and Carr (1906). *Ergotamine* was found by Stoll (1920). *Ergometrine* was found independently by four groups of observers, Dudley and Moir, Thompson, Stoll and Burckhardt and Kharosch and Lagault (1935). *Ergosine* was isolated by Smith and Timmis and *ergocristine* by Stoll and Burckhardt (1937). All these on hydrolysis form *lysergic acid* ($C_{16}H_{16}O_2N_2$) or its amide *ergine*.



Ergotoxine

Ergometrine

Ergot owes its action mainly to (i) **Ergotoxine**, **Ergotamine** also **Ergosine** and **Ergocristine**, these four resembling each other and to (ii) **Ergometrine** (also called **ergonovine**), which are its active alkaloidal principles, the last being more soluble in water. Ergot also contains a smaller quantity of **Tyramine** and **Histamine** or **Ergamine**: these are the decomposition products of protein and are both alcohol and water soluble and not in quantity to exert much therapeutic action.

Ergotoxine and Ergotamine

GIVEN INTRAVENOUSLY, these have characteristic action. The most important is on the **uterine muscles**.

(1) **ERGOTOXINE** is used as ethanosulphonate by intravenous or intramuscular injection. It causes contraction of the **unstripped muscle fibres** especially of the blood vessel and the uterus. The action is only on the motor augmentors, the inhibitors remaining unaffected.

(i) By its *vascular action*, it contracts the smaller peripheral arterioles and raises the blood pressure. Prolonged administration causes vascular spasm with obliteration of the lumen by pouring in of a hyaline substance and the distal parts of the body may become gangrenous for want of blood supply.

Only the augmentory motor endings of the sympathetic system are excited and not very much the inhibitory ones, thus differing from adrenaline which excites the entire sympathetic endings, both augmentory and inhibitory. The action is less powerful, of longer duration and can be produced both by oral and hypodermic administration.

Further, the stimulation takes place only with small doses, big doses paralysing them. This paralysing action is best shown on the blood vessels. If after the administration of a moderate dose of ergotoxine which contracted the blood vessels, adrenaline is injected, the blood vessels dilate. This shows that ergotoxine affects only one set of the autonomic nerve-endings namely, the vaso-constricting set and adrenaline the both, the vaso-constricting and if this is not available, the vaso-dilating set (p. 619).

Ergotoxine and ergotamine have similar action but the former more effectively counteracts adrenaline effect. Ergosine is probably even more powerful but is not readily obtained.

(ii) By *uterine action*, it causes powerful contraction of the uterine muscles. (a) With a moderate dose, the contractions are stronger with slow relaxation and with many new subsidiary contractions : a prolonged effect on uterine irritability is also produced. These are due to the action on motor excitory nerve endings of the uterus. (b) With a bigger dose, contractions are more powerful and spastic without relaxation. As the muscles are directly acted on, isolated uterus responds in the same way as one in situ. The gravid uterus is more effected.

Therapeutically it is administered after delivery with complete expulsion of the placenta to prevent **post-partum hæmorrhage** : also used to induce quick involution of the uterus during puerperium. The vascular effect is very little. It is of some value in menorrhagia, 0.5 mg. intramuscularly daily, being useful.

It is less effective than ergotamine in migraine.

Over dose causes headache, depression and vomiting and prolonged administration, tendency to gangrene.

(2) **ERGOTAMINE** has similar *vaso-tonic* and *oxytocic* effects.

(i) It has like ergotoxine *sympatholytic effect* although less marked, causing vaso-motor reversal effect with adrenaline.

Its *vaso-tonic action* is especially marked on extracranial arteries and this action probably gives relief in **migraine**. The usual dose is 0.25 mg. intramuscularly, may be repeated hourly upto 3 doses : oral dose is 1 mg. hourly upto 6, may be given sublingually.

DIHYDROERGOTAMINE, a semisynthetic alkaloid obtained by hydrogenation of ergotamine is more preferred. It has only the vascular effect but *no uterine action* and is better tolerated : available in *solution* (1 ml. has 2 mg., dose 0.5 to 1 ml. 3 times daily) and in *ampoule* (1 ml. has 1 mg., 0.5 to 1 ml. subcutaneously or intramuscularly).

(a) *Migraine*.—In acute attacks, 0.5 to 1 mg. parenterally, may be repeated, followed by $\frac{1}{2}$ to 1 ml. *orally*, (this only may do in milder attacks) : this oral dose is also prophylactic, 1 to 3 times daily.

(b) *Herpes zoster*, 0.5 to 1 mg. parenterally daily for 6 doses may do : in mild cases, oral administration may be sufficient.

(c) *Headache* due to hypertension may have the above treatment.

(d) *Meniere's disease* : 0.5 to 1 ml. 1 to 3 times at intervals of 1 to 2 hours and in severe crisis, 0.5 mg. intramuscularly are given.

This is not to be used in the presence of coronary arteriosclerosis.

(ii) *Heart muscles* contract with slightly greater force increasing the cardiac output and this, combined with vascular contraction, raises the *blood pressure*.

Pulse-rate is at first increased and then diminished, partly from stimulation of the vagal centre in the medulla by the raised blood pressure and partly from the direct action on the heart muscles. But if the rate is much slowed, the blood pressure falls.

(iii) It has *oxytocic action* like ergotoxine and is used in the same way as ergotoxine and of all ergot preparations its action is most prolonged. It has further advantage of oral administration. Therapeutically ergotamine tartrate is usually used.

(iv) The *pupils* are contracted. As this is not counteracted by atropine, the action is direct on the muscles.

(v) *Respiration* is often much quickened in poisoning in some animals, due to the stimulation of the centre.

(vi) *Temperature* is often raised by ergotoxine in cats and rabbits probably due to increased heat formation and diminished loss. Ergotamine is much less active.

Tolerance : after repeated injections in animals, a moderate degree of tolerance is established.

Available as **ERGOTOXINE ETHANESULPHONATE** 1 mg. oral tablets and 0.5 mg. in 1 c.c. ampoules

GYNERGEN (*Ergotamine tartrate*), 1 mg. tablets and 0.5 mg in each ml. ampoules.

Ergometrine, $C_{19}H_{23}N_3O_2$

Ergometrine has action on the uterus (*oxytocic*) and on the blood vessels (*sympathomimetic*) but no inhibitory effect on adrenaline action.

It was long realised that the whole ergot preparation was therapeutically more prompt in action than the alkaloids, ergotoxine and ergotamine. The watery extract which has very little of these alkaloids was also effective.

Moir (1932) came to the conclusion that the characteristic effect of ergot was not due to either these or to tyramine or histamine but to a substance still unidentified. It was found that oral administration of ergotoxine and ergotamine did not cause any contraction of the uterus for an hour whereas the

watery extract of ergot was effective in about ten minutes. Dudley and others (1935) isolated this active substance now called *ergometrine* or *ergonovine*. This orally in 0.5 to 1 mg. dose causes uterine contraction in 5 to 8 minutes : intramuscularly in 0.25 to 0.5 mg. dose in 3 minutes and intravenously in 0.05 to 0.1 mg. dose in one minute.

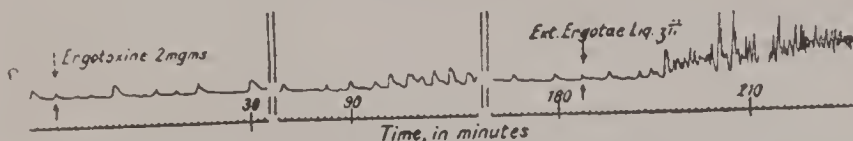


Fig. 60.—Comparison between ergotoxine 2 mg. by mouth and the liquid watery extract of ergot (1914 B.P.) 120 minims by mouth. The tracing was continuous but only sections of it are shown, (Moir 1932). The latter, the watery extract, is obviously more effective and prompt. *B.M.J.*, June, 1932.

Thus, compared with the other alkaloids, ergometrine has been found to be more **prompt** and **powerful** in action, does **not** **paralyse** the **sympathetic** nerve endings and is much **less toxic**. Although the blood pressure is moderately raised, there is no vasomotor reversal effects and no inhibition of adrenaline action (not sympatholytic). Its repeated administration does not cause gangrene of cock's comb.

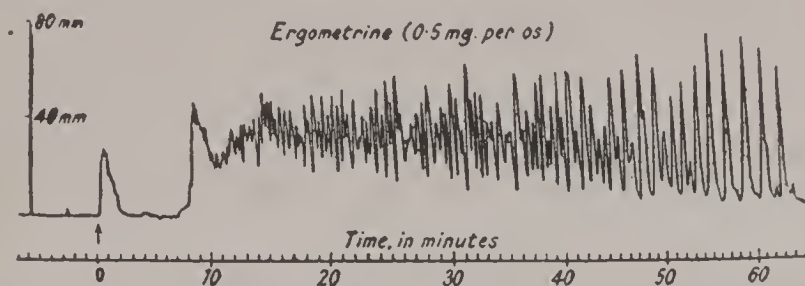


Fig. 61.—The tracing of uterine contraction made on the sixth day of puerperium showing the effect of 0.5 mg. of ergometrine by mouth. This undoubtedly has the best action on the uterus. (Dudley and Moir. 1935) *B.M.J.*, March, 1935.

With a moderate dose, only the uterine action is obvious : the tone, rate and amplitude of contractions are increased.

Symptoms of over action are mainly from *central nervous system stimulation* (weakness, tremors and convulsion) and *central sympathetic stimulation* (dilatation of the pupil, exophthalmos, standing of the hairs and quick cardiac action). Ergometrine therefore, appears to be better for oxytocic purpose than the previously known alkaloids.

[In practice, the ergot preparations are mostly prescribed for uterine action. Orally, the whole ergot product (the liquid extract) is usually given after childbirth and expulsion of the placenta. An initial dose of 20 to 30 minims of *extract* is followed

by 15 minims three times daily : *tablet* of prepared ergot may also be used. This prevents **postpartum hæmorrhage** and favours rapid involution of the uterus^{493, 194}. For immediate action, the most reliable ergot-product is 0.5 mg. of ergometrine in 1 c.c. of water alone or with $\frac{1}{2}$ c.c. of posterior pituitary extract (as pitocin) injected intramuscularly into the buttock].

Available as *Ergometrine Acid Maleate*, 0.5 and 1 mg. oral tablets and 0.5 mg. in 1 c.c. ampoules : for intravenous injection, 0.125 mg. in 1 c.c. ampoules.

Ergodex is a mixture of ergotoxine and ergometrine, available in 1, 4 and 16 oz. phials : DOSE 10 to 20 min. 3 or 4 times daily.

Neogynergen contains 0.25 mg. of ergotamine tartrate and 0.125 mg. ergometrine tartrate in tablets and ampoules. This has the prompt action of ergometrine with sustained action of ergotamine.

On the non-gravid uterus, the action is less certain. It may act as **emmenagogue** by increasing the uterine movements and sometimes control the bleeding of menorrhagia. But in bleeding from other places it is not suitable as its vaso-constricting effects on the blood vessels is associated with a rise in the blood pressure which more than counterbalances any possible beneficial effect that may follow.

Liquid ergot extract deteriorates on storage : so the preparation should not usually be more than one year old.

SUMMARY.—The main active principles of ergot are *ergotoxine*, *ergotamine* and *ergometrine*, all having oxytocic and vaso-tonic effects. These are mostly used as **oxytocic** ; ergometrine is most prompt but less sustained : ergotoxine and ergotamine take a little more time and *ergotamine* has more sustained effect : usually ergometrine-ergotamine combination is preferred to control post-partum hæmorrhage, subinvolution of the uterus also sometimes menorrhagia. Ergotoxine, in prolonged administration may cause blocking of small arterioles and peripheral gangrene and is not as frequently used. **Vasotonic effect** of ergotamine makes it useful in migraine, hypertensive headache and in Meniere's disease.

ERGOT POISONING.—*Acute poisoning* is comparatively uncommon but may follow the intake of a very big dose. The symptoms are of collapse with thready pulse, gastro-enteritis, coldness, tingling and itching of the skin, uterine and sometimes subcutaneous hæmorrhage and mental confusion ending in coma. Death follows from respiratory failure. Given in a therapeutic dose to a pregnant woman, ergot causes abortion. Even without abortion, fatal poisoning may occur.

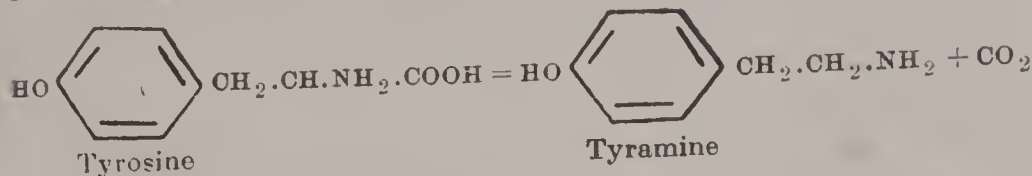
Chronic poisoning is due to prolonged intake of infected rye, formerly common among the poor people in Europe. The symptoms are either of slowly developing dry gangrene especially of the fingers and toes rarely of the internal organs or of mental languor, cramps on the limbs, itching and burning sensation in the skin, headache, giddiness and somnolence : sometimes periodic attacks of convulsion appear, rarely drifting to insanity.

(493) R
Ext. Ergot. Liq. min. 15
Sp. Vini Gallici. min. 30
Syr. Aurant. min. 60
Aq. Menth. Pip. ad. fl. oz. 1
One 3 times daily. Post partum
mixture.

(494) R
Quinin. Sulph. gr. 3
Acid. Sulph. Dil. min. 10
Ext. Ergot. Liq. min. 20
Aq. Chlorof. ad. fl. oz. 1
Post partum mixture.

Tyramine

Tyramine is a protein decomposition product and is formed from the amino-acid tyrosine by losing its carboxyl group :



It acts on the sympathetic nerve-endings like adrenaline and can be given by the mouth as it is not much destroyed by the digestive ferments. Its effect from a subcutaneous injection is immediate. The pulse is at first quickened and then slowed. The heart beats are made more powerful. The blood pressure is raised. The uterine muscles are also contracted, if gravid. But it has very little action on nongravid uterus. It causes contraction of other plain muscles which are relaxed by adrenaline because it is less active on the inhibitory mechanism. It is present in small quantity only in ergot preparations and is of no clinical importance.

Non-official Preparations

ERGOTIN, solid extract of prepared ergot. **DOSE**, 2 to 3 grs. Prepared by extraction with acidulated water in which alcohol is added⁴⁹⁵.

HYDRASTIS : *Extractum Hydrastis Liquidum*.—Contains 2% of hydrastine alkaloid. **DOSE**, 5 to 15 minims.

Hydrastine and Hydrastinine Hydrochloride.—**DOSE**, $\frac{1}{4}$ to 1 grain orally or hypodermically.

Hydrastis contains *hydrastine*, *berberine* and *canadine*. Berberine is bitter and therefore preparations of hydrastis act as *bitter stomachic* and *carminative* and for the same reason it is somewhat *antiperiodic*. But hydrastis is not much used for any of these purposes. It is chiefly used for chronic inflammation of the *mucous membranes*. Thus it is prescribed, in *menorrhagia* and *dysmenorrhœa*^{496, 497}. Hydrastine increases the tone, rhythmicity and the force of contraction of the uterus by direct action on the muscles. It has also direct action on the blood vessels constricting their muscular coat and, to a less extent, on the heart muscle, increasing the force of contraction. Blood pressure is raised and the pulse is slowed. Hydrastine is prescribed as pills with ergotin and cotarnine⁴⁹⁸, to control uterine bleeding. It also acts as an *astringent* : in dilute solution it is sometimes used as a wash for various chronic inflammatory conditions in

(495) B

Ferr. Sulph. Exsic. gr. 1

Ergotin. gr. 2

Ext. Nuc. Vom. Sicc. gr. $\frac{1}{4}$

Glycer. Trag. q.s.

Pil. For menorrhagia.

(496) B

Hydrastin. gr. $\frac{1}{4}$

Ergotin. gr. 1

Ext. Cimicifugæ gr. $\frac{1}{2}$

Pil. For menorrhagia.

(497) B

Ext. Hydrastis Liq. min. 10

Ext. Ergot. Liq. min. 15

Ext. Asok. Liq. min. 60

Syrupus min. 60

Aq. ad. fl. oz. 1

Mix : 3 times daily for menorrhagia.

(498) B

Ext. Cannab. Ind. gr. $\frac{1}{4}$

Ergotin. gr. 1

Hydrastin. Hydrochlor. gr. $\frac{1}{2}$

Cotarnin. Hydrochlor. gr. $\frac{1}{4}$

Glycer. Trag. q.s.

Pil. For painful menorrhagia.

the nose, ear, throat, urethra and vagina. Less commonly, it is used for various chronic and indolent ulcerative conditions in the skin.

VIBURNUM, Black haw.—A liquid extract is prepared by percolating the dried bark of viburnum with 70% of alcohol and is given in 60 to 120 minims doses. The active principle is a glucoside *Viburnin*.

The Indian variety, *Viburnum foetidum*, *Shirporna-jaya*, may be a substitute.

It depresses the motor functions of the spinal cord and causes a certain amount of muscular paralysis and loss of reflexes. It is depressant to the heart, reducing the blood pressure.

For its *sedative action* it is often prescribed in various painful conditions of the uterus⁴⁹⁹ as dysmenorrhœa, threatened abortion and in menorrhagia. It is also given in earlier months of pregnancy to prevent recurrent abortions.

SARCA INDICA (*Asoka*) and **ABROMA AUGUSTA** (*Olat Kambul*) of the Ayurveda have reputation in uterine diseases, the former in menorrhagia⁵⁰⁰ and the latter in dysmenorrhœa relaxing uterine musculature and are sometimes prescribed. But no definite active principles have as yet been isolated.

XVI. IMMUNE THERAPY

In addition to various specific chemotherapeutic drugs and antibiotics, certain therapeutic agents of biological nature are used against some well-defined bacterial infections and consist of an *antitoxic* or *antibacterial* substance (as a **specific serum**); some killed bacteria or *bacterial toxin* (as a **vaccine**) or a *bacteriolysin* (as a **bacteriophage** or a similar bacteriolytic agent), introduced from outside with the above specific object.

Specific Sera

Bacteria growing in laboratory culture or in an animal body, sometimes produce a soluble toxin in the medium itself called **exotoxin** (as in the case of diphtheria, tetanus, gas gangrene, and probably Shiga-bacillary dysentery, staphylococcus aureus, streptococcus scarlatina and meningococcus) or the toxin remains in the substance of the bacteria itself called **endotoxin** as in most other organisms.

If a person gets a bacterial infection and he finally recovers, he is often immune to a second attack at least temporarily (**active immunity**). This immunity may be obtained artificially also by injection in suitable graduated doses of the same bacteria (vaccine). Now if the serum of this person be injected into another person in sufficient quantity, the latter also becomes temporarily immunised (**passive immunity**). Active immunity is attained slowly and is much more lasting, but the passive

(499) R

Sod. Brom. gr. 15

Ext. Viburn. Liq. min. 60

Syr. Aurant. min. 60

Aq. Aneth. ad. fl. oz. 1

For threatened abortion.

(500) R

Sod. Brom. gr. 10

Ext. Viburn. Liq. min. 60

Ext. Asok. Liq. min. 60

Tinct. Hyoscy. min. 30

Aq. Chlorof. ad. fl. oz. 1

For painful menorrhagia.

immunity is obtained at once and lasts only for one week to three months.

It has been found that active immunity of high potency is attainable in many lower animals also, by injecting the bacterial exo- or endotoxin in sublethal but in progressively increasing doses. This immunity producing substance is called **antigen**. When a high degree of immunity is reached, the animal is bled and the serum obtained therefrom is used for therapeutic purpose either for preventing (*prophylactic*) or for cutting short an infective process (*curative Sera*).

Of all animals, the horse has been found to be specially suitable for the above purpose partly on account of its size yielding a large amount of serum at a time and partly also for the high grade of immunity developing in it. The antigen is carefully prepared by growing the bacteria on a medium that will give it the highest degree of toxicity. The animal is carefully looked after and injected with gradually increasing doses of the antigen. When a high grade of immunity has developed, the animal is bled. The blood is collected in strict aseptic condition. The clear serum is separated by allowing the blood to clot. Or else, the blood is collected in potassium oxalate solution, the red blood corpuscles separated by centrifugalising and the fibrin from the clear plasma by adding calcium chloride. The clear fluid thus obtained is the specific serum. The corpuscles are then washed, mixed with normal saline and re-transfused into the animal. This enables the horse to recover quickly and yield a large supply of serum with a short interval.

NORMAL HORSE SERUM.—The serum of a healthy horse or a sheep which has not been previously immunised is also used. This containing serum albumin and serum globulins, fibrin ferment and also the natural crystalloids of the blood. This is useful *locally* on a septic wound surface, (its antitryptic substance counteracts the proteolytic action of pus on the growing epithelium), *orally* in gastro-duodenal ulcer or *subcutaneously* in various hæmorrhagic conditions. DOSE, 10 to 20 c.c.

CONCENTRATION OF THE SERA.—The *antitoxin* is mostly contained in the pseudo-globulin fraction of the serum. First euglobulin and fibrinogen are precipitated by $\frac{1}{3}$ rd saturation of the serum with ammonium sulphate and then pseudoglobulin is precipitated. This is collected freed from ammonium sulphate by dialysis, a requisite amount of sodium chloride is added to make 0.85% solution of it, filtered bacteria-free, standardised and put up for use. By removal of the redundant albumin and euglobulin fractions, the sera are readily tolerated without much serum sickness, and also act more promptly. Further, the same volume contains 3 to 4 times the antitoxin : so a large quantity of the active substance may be given by a single injection. In an *antibacterial serum*, the euglobulin fraction is more important and is not removed : the precipitate contains both euglobulin and pseudoglobulin : to this a requisite amount of sodium chloride is added to make 0.85% solution.

The dose of an antitoxin is described in *units*. One unit of the toxin is that quantity which, being injected, kills a guinea-pig weighing 250 gm. in 4 days. This is also called the minimum lethal dose or *M.L.D.* A unit of antitoxin is that amount which protects the guinea-pig if injected with 100 units of the toxin.

SERUM SICKNESS.—In some individuals, a subcutaneous injection of horse serum causes certain disturbances, appearing near about the eighth day or earlier. These are more or less generalised urticarial rash with troublesome pruritus, fever, pain and swelling of the joints, albuminuria and inflammation of the lymphatic glands. These usually persist for 2 to 5 days. These disturbances are more likely to appear in persons predisposed to asthma, urticaria and angioneurotic oedema (*susceptibility to protein allergy*). These are however uncommon in modern albumin-free concentrated sera. In a susceptible person, an intracutaneous injection of 0.25 c.c. of the serum in 0.85% sodium chloride solution is given. If a red wheal appears, progressing to form a vesicle, the serum should be given cautiously and never intravenously. This condition is also called *allergy*.

In some cases, if the serum is given intravenously, there may be immediate reaction or shock, shown by sudden collapse which passes off in a few minutes spontaneously or on the administration of adrenaline or ephedrine.

ANAPHYLAXIS.—When a serum or any foreign protein is injected into a person, a condition of hypersensitivity develops and if after 10 days or a much longer period, another dose of it is given, various symptoms of disturbances may appear almost immediately. These are urticaria, dyspnoea, cyanosis vomiting, cardiac weakness and even collapse. If it is required to administer a serum to a person who had previous injections of horse serum, the reaction for hypersensitiveness is tested as above. If this exists, which is manifested in half an hour, the patient is desensitized. He is given 0.025 c.c. of the serum subcutaneously and the quantity is doubled every half an hour. If 1 c.c. is tolerated, the serum may be given intravenously. If there is any symptom in the preliminary injections, the dose should be even more cautiously increased and with longer intervals.

TREATMENT.—For *urticaria* and *pruritus*, bath in sodium bicarbonate lotion ($\frac{1}{2}$ oz. to a gallon): calcium gluconate 20 grs. twice or 3 times daily orally or 5 c.c. of 10% solution intramuscularly; also solutions of adrenaline hydrochloride, ephedrine hydrochloride and atropine sulphate subcutaneously. For *heart failure*, adrenaline hydrochloride subcutaneously and sometimes intravenously: caffeine sodium benzoate, 3 to 5 grains is also sometimes given.

Sulphonamides and antibiotics have largely replaced the antibacterial sera. The antitoxic sera are still used.

THERAPEUTIC ADMINISTRATION.—The serum should be fresh and used within the specified date. It should be stored in cold, away from light.

(i) *Subcutaneously*.—The serum is sometimes injected into the loose tissues of the flank or of abdominal wall. In this way, 20 to 30 c.c. of it may be given in each side. But the rate of absorption is slow, taking 6 to 10 hours, the maximum concentration in the blood being reached in 72 hours. This is a serious drawback.

(ii) *Intramuscularly*.—The injection is given into the gluteals and less commonly into the thighs (*vastus externus*) or rarely into the deltoids. About 20 c.c. can be given in one place and the absorption is more prompt. The maximum concentration in the blood is reached in 24 hours. This should be the routine method of administration.

(iii) *Intravenously*.—In a very acute or severe infection, where a large quantity of serum is required and also a quick concentration of it in the blood, the serum may be given intravenously. On account of quick elimination of the sera, the intravenous administration is of temporary value only.

(iv) *Intrathecally*.—Lumbar puncture is made, the cerebro-spinal fluid is drained out to remove 20 to 30 c.c. and a slightly smaller quantity of the serum, previously warmed, is allowed to flow in by gravity. This method once popular in cerebro-spinal fever and in tetanus is now disappearing.

(v) *Orally*.—Serum is sometimes given by the mouth on empty stomach but the results are doubtful and so it should not be depended on unless local action is aimed at.

Vaccines

These are living but modified, dead and attenuated *bacteria* or bacterial products or *virus* as of rabies or cow pox, in sterile suspension often in physiological sodium chloride solution, given usually subcutaneously in a case of infection by the same type of organisms. The object is to stimulate the natural mechanism of *immunity-production* and by repeating the injection in gradually increasing doses, in a favourable case, the immunity is increased several hundred times. The following points must be remembered in vaccine therapy.—

(i) Immediately after the injection, there is a **negative phase**, in which the power of resistance to the infection is lowered shown by lowered opsonic index and a rise in the temperature.

(ii) If the dose is not overwhelmingly big, the rise in temperature settles in a day or so and the power of resistance goes up even above the previous level (**positive phase**) and by repeating the injections only at the height of such a positive phase, a considerable amount of immunity may be gradually built up.

(iii) The active immunity caused by a vaccine develops slowly, taking 2 to 3 weeks but it is more lasting. If however, the infection is generalised and the patient is very ill, the vaccine is of no use : it may rather do harm. The patient is

given, instead, the specific serum which produces immediate immunity. This later on is followed up, as the condition improves, by vaccine for the production of more lasting immunity.

(iv) As there are many sub-groups under each group of bacteria, an autogenous vaccine gives a better result than a stocked one. But a stock vaccine may be given as (a) a preliminary measure before the autogenous vaccine is ready, (b) where an autogenous vaccine cannot be prepared, (c) for prophylactic purposes and (d) also when an autogenous vaccine fails: a stock vaccine from a more virulent strain may be given with benefit.

(v) No second dose of the vaccine should be given till the negative phase of the first injection is sufficiently over.

(vi) Vaccines are used for *prophylactic* and *curative* purposes. For the former, a much higher dose is given causing some reactions. For the latter, the initial dose should be much smaller, being inversely proportional to the severity of the infective process. A child requires a proportionately smaller dose than an adult. Further, the dose should only be gradually increased the maximum being reached by the 6th or the 10th dose, causing mild or very little constitutional disturbance.

The immediate effects of a vaccine injection may be *local* (at the site of the injection), *general* (constitutional disturbances) and *focal* (at the site of the disease) reactions which in a favourable case should be progressively less following each injection.

THE MODES OF ADMINISTRATION OF A VACCINE

(i) A vaccine is usually given *subcutaneously* or *intradermally* at the outer side of the upper arm below the insertion of the deltoid where the tissue is loose. A fine sharp needle on a syringe is introduced flat under the cuticle and the fluid injected. This forms a marked wheal which slowly disappears.

If no severe reaction is caused by the first dose, later on $1\frac{1}{2}$ to twice of the previous dose may be tolerated. It should be repeated in a chronic case every 4 to 7 days and in an acute case, 2 to 3 days or even earlier.

(ii) *Oral* administration is not to be recommended. The dose is diluted with 120 to 240 minims of sterile water and is given on empty stomach in the morning, more useful in young children than in the adults.

BESREDKA's method of giving *bilivaccine* (one bile tablet followed 15 minutes after by one vaccine tablet, no food being given for one hour; three doses for three consecutive mornings) orally, for the prophylaxis of typhoid fever and cholera, is now nearly obsolete.

(iii) A stock vaccine is sometimes given *intravenously* to cause constitutional disturbance of the nature of protein shock in various chronic inflammatory conditions, especially arthritis, obstinate skin diseases, gonorrhœa and also in filariasis. (PYRETOTHERAPY).

VARIETIES OF VACCINES

(i) **Plain vaccine.**—The micro-organisms are killed by exposing to heat of 55° to 66° for one hour and emulsified in normal saline. After the necessary dilution, 0.5% phenol is added as a preservative. This vaccine may be *autogenous*, prepared from the bacteria of the infection in the patient or *stock*, bacteria being obtained from several different patients. The organisms may be one or of several varieties : *plain* or *mixed* vaccine. The official vaccines are of this type.

(ii) **Sensitised vaccine (Sero-bacterin).**—The bacteria are emulsified with the corresponding immune sera and these are next washed free of the sera. This is believed to lessen the toxicity and the initial dose of the vaccine may be 10 to 20 times higher. Further, it does not give rise to much local and general reactions and has no negative phase. It is more suitable in generalised infection where a quicker immunity response is wanted.

(iii) **Detoxicated vaccine.**—Here the endotoxin of the bacteria is removed or is treated with formalin or/and alum (*toxoid* or *anatoxin*) without disturbing the bacterial cell substance. The result is that a larger dose may be given without causing severe reaction. A toxoid is largely used for prophylactic use against a probable bacterial infection.

(iv) **Phylacogens.**—These are prepared from the solutions of several bacterial bodies capable of easy assimilation by the tissues. The composition is complex, containing 50% of the autolytic products of the bodies of staphylococci, streptococci, pneumococci, *B. pyocyaneus*, coli, diphtheria and streptococci of rheumatic fever and erysipelas with 50% of the specific organisms. The idea underlying the making of such a complex mixture is that in a large number of cases an infection is really multiple, requiring a mixed antigen.

(v) **Immunogens.**—These are vaccines prepared from bacterial washings of a 18 to 24 hours' agar growth, believed to be better antigenic than vaccines prepared from broth culture. These are given subcutaneously daily or every other day in acute infections as pneumonia, gonorrhœa, erysipelas, rheumatic fever and also in various mixed infections. The initial dose is 0.1 or 0.2 c.c. intradermally. These are getting obsolete.

OFFICIAL SERA AND VACCINES

Six of the sera, antitoxins (see p. 53), seven toxins (see p. 60) and ten of the vaccines (see p. 63) are introduced in the British Pharmacopœia.

1. DIPHTHERIA

1. **Antitoxinum Diphthericum** (*Antitox. Diphtheric.*), Diphtheria Antitoxin.

This is a serum or a preparation from serum containing the antitoxic globulins or their derivatives which have the power of

neutralising the toxin formed by the specific infective organisms *Corynebacterium diphtheriæ*.

A special strain of diphtheria bacilli originally isolated from the throat of a diphtheria patient and subsequently cultured in the laboratory for a long time, is cultured in peptone broth. To this 0.5% carbolic acid is added and 24 hours after, this is filtered through paper pulp and if not sterile, it is again filtered through Berkfeld filter. The filtrate contains the toxin. This is so standardised that 0.1 c.c. kills a good-sized guinea pig. This is subcutaneously injected to a specially prepared horse. If no severe reaction, injection is given intravenously every 2 to 3 days, starting with $\frac{1}{2}$ c.c. and gradually increasing till 500 c.c. is reached. Usually at the end of the fourth or the fifth week the blood develops the full quantity of antitoxin. The horse is then bled and the serum contains the antitoxin. From this the specific globulin is separated, dissolved in normal saline, a preservative is added and put up in sterile ampoules.

STRENGTH.—The liquid preparation should have no less than 400 units per ml. and the solid preparation, 5000 units per gm.

DOSE, by injection, *prophylactic*, 500 to 2000 units and *therapeutic*, not less than 10,000 units : repeated as necessary.

2. Toxinum Diphthericum Calefactum, Schick control. This is Schick test toxin, heated to a temperature of not less than 70°C for not less than five minutes.

DOSE, by intradermal injection, 3 minims or 0.2 ml.

3. Toxinum Diphthericum Diagnosticum, Shick test Toxin.

This is the sterile filtrate of the diphtheria toxin from broth culture which, after being allowed to mature, is diluted before use so that 0.2 ml. contains the test dose.

DOSE, by intradermal injection, 3 minims or 0.2 ml.

4. Toxinum Diphthericum Detoxicatum, *Diphtheria Prophylactic*. This is the sterile filtrate or material derived from the filtrate, of a broth culture of *Corynebacterium diphtheriæ* whose toxicity has been reduced low but has the requisite antigenic properties. This has been prepared in the following and in other forms :

(a) **FORMOL TOXOID** or **ANATOXIN**, (F.T.), prepared by treating the filtrate with formaldehyde to remove toxicity.

DOSE, by intramuscular injection : the volume indicated on the label as the dose, on two or three occasions, at intervals of not less than 4 weeks in the case of first two and at the interval of not less than 2 weeks if the third is used.

(b) **ALUM PRECIPITATED TOXOID**, (A.P.T.) is prepared by treating the filtrate with formaldehyde, adding alum in the proportion necessary to produce a suitable precipitate, separating the precipitate and washing and suspending it in physiological sodium chloride solution.

DOSE, the first dose of 0.2 to 0.5 ml. is followed at an interval of not less than four weeks by a second dose of 0.5 ml.

(c) **DIPHTHERIA TOXOID-ANTITOXIN MIXTURE (T.A.M.)**, prepared by adding to (a), a small quantity of diphtheria antitoxin sufficient to neutralise all unaltered toxins.

Dose, three doses, each of 1 ml. at an interval of not less than four weeks between the first and second doses, the third dose being given at an interval of not less than two weeks after.

(d) **DIPHTHERIA TOXOID-ANTITOXIN FLOCCULES, (T.A.F.)**, prepared by adding diphtheria antitoxin to the toxoid, equivalent to 80% of it, separating the floccules, washing and suspending them in physiological saline solution.

Dose, as of *Toxoid-Antitoxin mixture*.

A.P.T. is slowly absorbed and is said to cause less reaction and better immunity response. (Two doses are preferable although even one dose may do). It is more frequently used in children. If it causes reaction, T.A.F. is chosen (three doses are required) which is least likely to cause any. This is used in adults. The injections are given intramuscularly. F.T. and T.A.M. are not so much used.

Therapeutic Uses

(1) *Prophylaxis*.—Children below 9 months are usually immune. Those between 9 months and 8 years are most susceptible and if contact of a case, should all be immunised. Above that age, only those showing positive Schick's test are immunised as follows :

Subcutaneous injection of 500 to 1000 units of the serum gives immediate protection lasting for about 3 weeks (passive immunity).

This method may sometimes be useful in the contacts living in the same mess or boarding house. As this causes hypersensitiveness to serum, the subsequent serum treatment is made difficult and consequently not favoured.

(a) For *children*, two doses of 0.5 ml. of A.P.T. are given intramuscularly with at least 4 weeks' interval (even several months) : the initial dose may be 0.2 ml. (b) For *adults* who are more liable than children to reactions, T.A.F. in 3 injections of 1, 1 and 1.5 ml. are given with 3 to 4 weeks' interval. Susceptibility to reactions may be first tested by 0.2 ml. of diluted toxoid. The active immunity develops in 6 weeks. If immunisation is done in the 9th month, a supplementary dose of 0.5 ml. may be given at the beginning of school life.

SCHICK'S TEST.—Diphtheria test toxin, in 0.2 c.c. of normal saline is injected intradermally into the inner surface of the forearm. On the other side, the heated toxin is injected in the same way. Absence of reaction with the active toxin indicates the presence of more than 1 200 unit of antitoxin per c.c. of blood which is the sign of immunity. Those individuals that react to Schick's test, by forming a red flush with induration 1 to 2 cm. in diameter, in 24 to 36 hours lasting for about one week should be given the prophylactic inoculation.

(2) For the *curative purpose*, the concentrated antitoxic serum is injected as soon as the clinical diagnosis is made. The

serum effectively neutralises the toxin in circulation but is less active on that which is fixed in the cells of the body : this is the special reason for its early administration. The initial dose (a) in a moderately severe case, seen on the first day, is 8,000 to 10,000 units. (b) If seen on the 2nd day or after, 12,000 units or more, even 50,000 units, according to the severity of the toxæmia : may be repeated 12 to 24 hours after, usually once. (c) A laryngeal case requires a comparatively bigger dose : seen early, usually, 20,000 units for 2 days. (d) A severe nasopharyngeal case especially with laryngeal involvement, requires 60,000 to 80,000 units partly intramuscularly and partly intravenously. In fixing up the dose, the *degree of toxæmia* is the factor to be mostly considered and the serum is usually given intramuscularly and in severe cases, intravenously.

[Diphtheria antitoxin is undoubtedly one of the most remarkable therapeutic achievements. The temperature comes down, toxæmia gets less, membrane slowly disintegrates, dyspnœa and dysphagia get better and the ultimate mortality rate considerably lessens].

2. DYSENTERY

Vaccinum Dysentericum (*Flexner*), Dysentery Vaccine.

Vaccinum (*Flexner*) contains in 1 ml. 100 millions of each of V, W, X, Y and Z types of *Flexner* bacilli.

Dose, *prophylactic*, first dose, 0.5 ml. : second dose after 7 to 14 days, 1 ml. : third dose, after 7 to 14 days, 1 ml.

SERUM ANTIDYSENTERICUM (*Shiga*), Not official.

It is the specific antitoxic globulin, prepared very much like diphtheria antitoxin. The bacillary bodies or the whole culture (the filtrate and the bacteria) are used for immunising the horse.

Dose, 4,000 to 10,000 units or more. By injection.

Anti-dysentery serum (*Shiga*), is injected in 30 to 100 c.c. doses, partly intramuscularly and partly intravenously, within 48 hours of the onset of the disease, after which it is less effective. It is moderately *antitoxic* and neutralises the toxin of *Shiga* infection which is mainly an exotoxin. But sulphonamides (p. 365), have largely replaced it.

Prophylactically, 10 millions of *Shiga* and 50 millions of *Flexner* vaccines are sometimes given. This needs repetition 1 to 2 weeks after.

3. GAS GANGRENE

This condition was often seen in street injuries with markedly lacerated wounds. The infective organisms, 3 *Clostridia* cause extensive gangrene with gas formation inside the tissues. These sometimes cause suppurative peritonitis after abdominal operation for acute appendicitis and intestinal obstruction. The antitoxins have both prophylactic and curative values. Penicillin is also of great curative value.

1. Antitoxinum Œdematiens (*Antitox. Œdemat.*), Gas-gangrene Antitoxin (œdematiens).

This is a serum or a preparation of serum containing antitoxic globulins or their derivatives which have the specific power of neutralising the toxins of *C. œdematiens*.

It is prepared in the usual way from the blood serum of an animal (horse) immunised by graded injections of the sterile filtrate from a culture of *Clostridium œdematiens*. The antitoxic globulins formed have the specific power of neutralising the toxins of the infection.

Dose. *Prophylactic*, 10,000 units; *Therapeutic*, not less than 30,000 units, by injection.

2. Antitoxinum Septicum (*Antitox. Septic.*), Gas-gangrene Antitoxin (septicum).

This is the globulin or a derivative of globulin with specific neutralising power of the toxins of *V. septicum*.

It is prepared in the usual way by immunising the animal with sterile filtrate from a culture of *Vibrion Septique*. The antitoxic globulins have the power of neutralising the specific toxin.

Dose. *Prophylactic*, 5,000 units; *Therapeutic*, not less than 15,000 units by injection.

3. Antitoxinum Welchicum (*Antitox. Welchic.*), Gas-gangrene antitoxin (*perfringens*).

This antitoxic globulin or preparation from globulin has the specific power of neutralising the toxins formed by *C. perfringens*.

In all cases, these are dissolved in sterile normal saline, a preservative is added and put up in ampoules.

Dose. *Prophylactic*, 10,000 units by injection. *Therapeutic*, not less than 30,000 units by intravenous injection.

4. Antitoxinum Œdematiens Compositum (*Antitox. Œdemat. Co.*), Mixed gas-gangrene antitoxin.

Prepared by mixing gas gangrene antitoxin (*œdematiens*), gas-gangrene antitoxin (*perfringens*) and gas-gangrene antitoxin (*septicum*).

POTENCY.—The first two have not less than 1000 units per ml. and the third, 500 units per ml.

Dose. *Prophylactic*, (a) gas-gangrene antitoxin (*œdematiens*) not less than 10,000 units; (b) gas-gangrene antitoxin (*perfringens*), not less than 10,000 units and (c) gas-gangrene antitoxin (*septicum*) not less than 5,000 units.

Therapeutic, (a) and (b) not less than 300,000 units and (c) not less than 15,000 units, repeated as required.

The combined vaccine is usually used both in prophylaxis and in treatment because it is not often possible to make out the exact nature of the infective organisms. Penicillin (p. 370) and sulphonamides (p. 361) are also useful.

4. PLAGUE

1. Vaccinum Pestis (*Vaccin. Pest.*), contains in 1 ml. 2000 million organisms (*P. pestis*).

Dose, 8 to 15 min. or 0.5 to 1 ml.

2. *Vaccinum Pestis Formolysatum* (*Vaccin. Pest. Formol.*), Haffkine's Plague Vaccine : IND. PHARM. LIST.

Formolised Vaccine of *P. pestis* having the minimum mouse protection dose of 0.004 ml. or less.

Dose, 1 ml. as the first dose and repeated after 7 to 10 days.

Plague Vaccine is given by hypodermic injection for *prophylaxis* against plague infection : two doses (0.5 and 1 ml., may be given at 7 to 10 days' interval which may cause reaction local and constitutional. Protection is obtained for about one year. No specific serum of dependable value is available : *sulphonamides* (p. 355) and *streptomycin* (p. 378) are more promising.

5. STAPHYLOCOCCIC INFECTION

1. *Toxinum Staphylococcicum Detoxicatum* (*Toxin. Staphylococc. Detoxicat.*), Staphylococcus Toxoid.

It is the sterile filtrate or derived from filtrate of a culture of toxicogenic *staphylococcus*, the toxicity being reduced low by chemical treatment, but the antigenic power remaining efficient. Used undiluted or diluted with injection of sodium chloride.

Dose by intramuscular injection, $\frac{3}{4}$ minim increased to 15 minims or 0.05 ml., gradually increased to 1 ml.

2. *Vaccinum Staphylococcicum* (*Vaccin. Staphylococc.*), Staphylococcus vaccine.

This contains in 1 ml. 100 to 1,000 million staphylococci (*Staphyl. aureus*).

Dose, *therapeutic*, 10 to 1000 million organisms at the intervals of three to seven days.

(i) A large variety of *localised* septic processes as boils, carbuncle and many pustular eruptions are due to staphylococci. (ii) Staphylococci may be *secondary invaders* in influenza ; these may cause bacterial endocarditis and sometimes septicæmia : metastasis may cause pyæmic abscesses, perinephric inflammation, osteomyelitis and septic arthritis. An *autogenous* vaccine is useful ; the usual initial dose is 25 millions. *Stocked* staphylococcic vaccine is also used but staphylococcus toxoid is more preferred. In many cases of impending suppurative process, a mixed vaccine of polyvalent streptococci and staphylococci is useful in aborting it.

These have now been largely replaced by sulphathiazole and penicillin especially in severer infections and in septicæmia.

6. TETANUS

1. *Antitoxinum Tetanicum* (*Antitox. Tetanic.*), Tetanus antitoxin.

It is serum or preparation from serum containing the antitoxic globulin or their derivatives, prepared in the same way as diphtheria antitoxin by immunising a horse with the specific toxin of *C. Tetani*.

Dose, *Prophylactic*, not less than 3,000 units. *Therapeutic* not less than 100,000 units.

2. *Toxinum Tetanicum Detoxicatum* (*Toxin. Tetanic. Detoxicat.*), Tetanus toxoid.

Tetanus toxoid is the sterile filtrate of a culture on a suitable medium of *Clostridium tetani* or material derived therefrom, the specific toxicity of which has been completely removed by the action of chemical substance in such a manner that it retains efficient properties as an immunising antigen. There are two varieties.

(a) TETANUS TOXOID in simple solution and (b) ALUM-PRECIPITATED TETANUS TOXOID: the former is prepared by treating the filtrate with formaldehyde and latter, by adding alum to tetanus toxoid in simple solution to produce the precipitate which is washed and suspended in physiological sodium chloride solution.

Dose by subcutaneous or intramuscular injection, 8 to 15 minims or 0.5 to 1 ml. followed after an interval of not less than 6 weeks by a second dose of 15 minims or 1 ml.

The serum is antitoxic: (i) for *prophylaxis*, (a) one dose only of 3000 units is given intramuscularly and better repeated, especially in severer cases, twice at weekly intervals. With a much lacerated wound, mixed gas-gangrene antitoxin is also given at the same time. The immunity is short-staying but is essential in an emergency giving immediate protection. (b) Recently the *toxoid* is more used: 1 c.c. of the toxoid is given twice at the interval of 6 weeks (this is now the routine in British Army) intramuscularly and the protection lasts for about 2 years.

(ii) But when the symptoms have already developed and the toxin is fixed in the nerve tissue, the benefit is not as pronounced. In such cases the serum should be given in very big doses: 200,000 units intravenously and 80,000 units intrathecally and if the wound involved a limb, a further 10,000 units injected into the tissues on the proximal side. As the antitoxin is slowly excreted, no further administration of the serum is needed in 7 days. If the wound is extensive 50,000 units should be given intravenously afterwards once a week (Gow and Scott, 1950).

For preventing mixed infections especially pulmonary, penicillin (p. 375) and for causing muscular relaxation, tubocurarine (p. 569) and mephenesin (p. 567) are prescribed.

7. TUBERCULOSIS

1. *Tuberculinum Pristinum* (*Tuberculin. Prist.*), Old Tuberculin.

Tubercle bacilli are grown in a fluid medium containing 5% glycerin at 37°C for six weeks or more. This is concentrated in water-bath to 1/10th of its original volume and filtered. A transparent, yellowish-brown, viscous fluid is obtained.

Dose, 1/6000 to 1/60 minim or 0.00001 to 0.001 ml. intradermally, diagnostic.

(Old tuberculin with suffix T. is the human type but with suffix P.T., is the bovine type).

2. *Tuberculini Derivativum Proteinicum Purificatum* (*Tuberculin Deriv. Protein. Purif.*), Tuberculin P.P.D.

This is prepared by fractional precipitation with a suitable protein precipitant of a fluid medium on which human type of tubercle bacilli has grown. Dissolved in a suitable buffer solution at a concentration not exceeding 0.08 mg. of nitrogen per ml. or if the dry powder is used, 5 mg. in each ml. : the potency is equivalent to the standard preparation of old tuberculin : supplied as powder or sterile tablets.

Dose, *Diagnostic* 0.1 ml. of a solution equivalent to 0.0001 ml., 0.001 ml. and 0.01 ml. of standard preparation of old tuberculin.

3. *Vaccinum Tuberculinum* (*Vaccin. Tuberculin.*), Tuberculin Vaccine, New Tuberculin.

Dose, *Therapeutic*, 0.000001 mg. to 0.1 mg. at the intervals from three to seven days.

Koch first introduced tuberculin with great hopes but now it is known that it has very little antigenic property and is sinking into oblivion : 1/400000 mg. or even less of the new tuberculin is sometimes given in localised tubercular infection as in lupus, gland, bone or joint tuberculosis. If there is no reaction, either local or constitutional, the dose is slowly increased. It is of value in some cases of bronchial asthma probably as non-specific antigen.

But more often old tuberculin is used for *diagnostic purpose*. An infection by tubercle bacilli renders the tissues hypersensitive to tubercular toxin if this is introduced from outside parenterally into the system. The clinical manifestation which is the specific sign of a pre-existing infection is *local* at the site of application usually on the skin also *systemic* (causing some febrile reaction).

(a) *Von Pirquet Test*.—A part of the skin of the forearm is sterilized with alcohol and ether : 2 places in it are scratched with a sterile needle without drawing blood. Into one of these, a drop of 25, 50 or 100% solution of old tuberculin is applied and into the other, a drop of normal saline control. If the reaction is positive, a red swelling forms within 24 to 48 hours. (b) Or in one place in the forearm, a percutaneous injection of 0.1 c.c. of normal saline and into another close by, the same quantity of 1 in 10,000 solution, increased, if necessary to, 1 in 1,000 solution of old tuberculin (often as tuberculin P.P.D.) are given. Positive reaction appears within 24 to 48 hours, shown by a red macular swelling (*Mantoux test*). (c) Tests are also performed by direct application of undiluted tuberculin on the skin held on by sticking plaster (*patch test*), by *subcutaneous injection*, rubbing into the skin in the form of an ointment with lanolin (*Moro's test*) or by dropping into the conjunctival sac (*Calmette or Wolff-Eisner's test*) of a solution of old tuberculin.

The evidence of positive reaction in each is local inflammation at the site. In clinical practice, first two tests are often performed.

These are of value in doubtful cases of pulmonary tuberculosis. Pirquet's test is more popular but except in 1 to 2 years of life it does not indicate active disease and may be positive in a large number of adults who had any tubercular infection in childhood. This may be absent also in cases of tuberculosis with an acute intercurrent disease.

OTHER TUBERCULINS.—*New Tuberculin*, T.R. (the virulent bacilli are dried in vacuo, ground up, washed and the soluble fraction diluted), *Tuberculin B.E.* (the entire body substance of the bacilli are ground up

and emulsified): *Tuberculin A.F.* (the bacilli are cultured in a special albumose and peptone-free medium).

B.C.G. (*Bacille Calmette-Guerin*) vaccine (attenuated live bacteria) is prepared by culturing tubercle bacilli on potato and glycerinated veal broth or modification, the toxicity being thereby much lessened. It is more used in France and Scandinavian countries for *prophylaxis* on very young children. Reports are encouraging but not yet proved unequivocally satisfactory.

8. TYPHOID FEVER

Vaccinum Typho-paratyphosum (*Vaccin. Typho-paratyphos.*), Anti-typhoid-paratyphoid Vaccine. T.A.B. Vaccine.

This is the sterile suspension of killed *B. Typhosus*, *B. paratyphosus A* and *B. paratyphosus B*. One ml. of it contains 1,000 million of *B. typhosus* and 500 million of each of *B. paratyphoid A* and *paratyphoid B*. The bacteria are grown on a solid medium for 24 hours, suspended in physiological saline solution, sterilised by heating for one hour to 55°C and put up in ampoules adding 0.5% of phenol as a preservative. This should not be older than 18 months after preparation.

Dose, *prophylactic*, subcutaneously, 0.25 to 0.5 ml. (first dose) and 0.5 to 1.0 ml. (second dose) 7 to 21 days after.

The specific typhoid serum or vaccine is of no dependable curative value. For *prophylaxis*, the T.A.B. vaccine is given: usually $\frac{1}{2}$ c.c. of it is followed by 1 c.c. a week or two after. A sharp reaction may follow which settles within 24 hours. Immunity takes 3 to 4 weeks to develop and lasts for a year. One dose given yearly keeps up the immunity.

BILIVACCINE.—This also gives some protection. Besredka thought that the intestinal mucous membrane was the first line of defence against an intestinal infection. The immune bodies are, therefore, more likely to be produced by the local application of the bacteria therein than into the skin.

T.A.B. vaccine is sometimes given intravenously for causing protein shock (*pyretotherapy*) and is helpful in chronic inflammatory conditions as chronic lymphangitis, arthritis, obstinate skin diseases and filariasis.

9. OTHER VACCINES

1. **Vaccinum Acnes** (*Vaccin. Acne.*), Acne Vaccine.

This contains in 1 ml. 20, 100 or 1,000 million acne bacilli.

Dose, *therapeutic*, 5 to 1,000 million organisms at intervals from three to ten days.

In *acne vulgaris*, acne vaccine or combined acne and staphylococcal vaccine is given hypodermically in graduated doses for a period of about a month and may be combined with sulphoamides orally.

LOCALLY, pus should be squeezed out of the comedones and a mild sulphur (p. 216) or calamine (p. 436) lotion applied.

2. **Vaccinum Cholericum** (*Vaccin. Choler.*), Cholera Vaccine.

Cholera Vaccine contains in 1 ml. 8,000 million cholera vibrios.

Dose, *Prophylactic*, (first dose) 0.5 ml. and (second dose) 1 ml. often after an interval of 7 to 14 days.

Cholera Vaccine is of great *prophylactic value* and is frequently used for mass inoculation especially during an epidemic. Two injections are necessary. The immunity produced is maintained for six months only and so it has to be given twice a year, 0.5 ml. in the subsequent administrations.

Usual practice is to combine it with T.A.B. Vaccine (*T.A.B.C. Vaccine*), and given once a year and cholera vaccine only six months after each combined injection.

3. *Vaccinum Pertussis* (*Vaccin. Pertussis*), Whooping cough vaccine.

This contains in 1 ml. 1,000 to 10,000 million Whooping cough bacilli (*H. pertussis*) in the cultural condition of phase 1.

Dose, Prophylactic. 1,000 to 20,000 million organisms on four or five occasions at intervals of from one to seven days.

Therapeutic : 500 to 10,000 million organisms at intervals of one to seven days.

Prophylactic inoculation of children below 10 years with the whooping cough vaccine has given a moderately hopeful results. *Therapeutic administration* also sometimes helps.

Diphtheria toxoid and pertussis combined vaccine is available and at one prick protection against both may be obtained.

Other *therapeutic measures* are (i) *antispasmodics* as belladonna, opiates, phenobarbitone, phenazone, bromides and ephedrine and (ii) *saline expectorants* with a plenty of sod. bicarb. and sometimes pot. iod. also

COMMERCIAL PREPARATIONS

WHOOPING COUGH ALUMPRECIPITATED VACCINE (Organisms are killed with formalin and precipitated by alum), each c.c. containing 20,000 million organisms : 3 injections of 0.5, 0.5 and 1 c.c. are given at four weeks interval.

DIPHTHERIA PERTUSSIS PROPHYLACTIC, each c.c. contains at least 1×10^8 diphtheria prophylactic and 20,000 million *H. pertussis* : three injections are given, 0.5, 0.5 and 1 c.c. at 4 weeks interval.

TETANUS TOXOID may also be mixed with this.

Vaccinum Typhi Exanthematici (*Vaccin. Typh. Exanth.*), Typhus vaccine.

Typhus Vaccine is prepared by (a) culturing virulent rickettsiæ in fertile yolk sac or obtained (b) from the lungs of small rodents and peritoneal cavities of gerbils having rickettsia infection. Vaccine is the sterile suspension of killed rickettsiæ heated with 0.2 to 0.5% formaldehyde. Should be stored in dark at 4° and this maintains potency for one year.

Dose, 4 to 15 minims or 0.25 to 1 ml. by subcutaneous injection.

Rickettsia vaccine has been found of *prophylactic value* for typhus infection especially of louse borne and of murine typhus. A dose of 0.5 to 1 ml. is given subcutaneously weekly for three weeks. The protection is partial and the disease may appear in mild form with less mortality.

Effective *therapeutic measures* are *aureomycin* and *chloromycetin* orally (p. 379).

10. VIRUS INFECTIONS

1. *Vaccinum Febris Flavæ* (*Vaccin. Febr. Flav.*), Yellow fever vaccine.

Yellow Fever Vaccine is a serum free aqueous suspension of chick embryo tissue infected with a strain of Yellow fever virus 17D, avirulent but antigenic for man : supplied in dry sterile powder to which water for injection or injection of sodium chloride is added immediately before use. It should be stored at 0° or lower in a dark place, which maintaining potency for about 3 months.

Dose, not less than 500 LD₅₀ doses, by subcutaneous injection.

The vaccine containing living virus is issued in freeze-dried powder in ampoules containing 5 and 20 doses. This is dissolved in sterile normal saline and injected subcutaneously. Reactions are rare except in persons susceptible to egg or chick protein. This has been found to give protection to persons liable to exposure to yellow fever infection. The immunity response is obtained in 10 days and persists for 2 to 4 years. One injection is usually sufficient, may be repeated every 4 years.

2. *Vaccinum Vacciniæ* (*Vaccin. Vaccinæ*), Vaccine lymph.

The skin of the belly of a carefully selected animal usually calf is shaved, cleaned and inoculated with the virus from another animal by scarification. After several days, the vesicles form and when these are mature, the lymph from inside are collected with thorough aseptic precautions, tested for septic organisms, mixed with glycerin and put up in capillary tubes.

This is a viscid, colourless liquid, containing opaque white matters in suspension. This should be kept in a cold chamber at 0°. If kept between 5° to 10°C it keeps for 2 weeks ; if above this temperature, for 7 days only.

Dose, 1 minim or 0.06 ml. by scarification.

Jenner in 1798 found that cow-pox of vaccinia infection gave immunity to small-pox and he introduced the practice of vaccination. In 1902 Copeman showed that the two diseases were allied, for when the virus of small-pox was given to a monkey and a calf was vaccinated from the monkey, cow-pox developed in the calf.

The vaccination is the most dependable preventive of small-pox. The primary vaccination should be done in the third month after birth and re-vaccination at the 7th, 14th and 21st year and also during an epidemic.

Immunity develops in a week or 10 days (more quickly than the disease itself) and lasts for about 10 years.

The outer side of the upper arm is cleaned with ether and rectified spirit. When completely dry, a drop of the lymph is put in two places, about $\frac{3}{4}$ of an inch apart and through it some parallel scratches are made with the lancet to cause red marks without drawing blood. In a successful case, a papule is usually formed in each of the two places on the third day which becomes vesicle on the 5th and pustule on the 10th day. This subsequently dries up forming a scab.

There may be complications : sepsis, generalised vaccinia, urticarial rash and more rarely encephalitis.

Encephalitis is more likely to be in unvaccinated children of school going age than in infants.

OTHER METHODS OF IMMUNE THERAPY

Four other methods of Immune Therapy are in practice ; three of these are against organisms and the fourth, against a toxin. These are less dependable.

(a) MEASLES.—The blood serum obtained from a convalescent on the 6th to 9th day of the drop in the temperature is injected intramuscularly into the contact for *prophylaxis*. The dose is 2 c.c. for each year of the age upto 10 c.c. This serum in bigger doses may be used for *curative* purposes also.

The *Placental Extracts* have been found to be of some value. Protein extracts composed of the globulins derived from the placenta and the blood contained in it from a healthy mother have been used (McKhann and Chu, 1935).* A concentrated serum is available in the trade : 2 c.c. is given for prophylaxis and 4 c.c. for treatment. This may cause constitutional reaction.

In ACUTE POLIOMYELITIS, convalescent serum and also normal adult human serum in 10 to 20 c.c. doses have been found to be of some value.

(b) RABIES.—**Vaccinm Rabies Carbolisatum** (*Vaccin. Rabies Carbol.*), Carbolised Rabies Vaccine. IND. PHARM. LIST.

DOSE, 2 to 10 ml. daily for 7 to 14 days according to the site and severity of bite and risk to the patient.

This virus is used for *prophylaxis* only. A rabbit is subdurally inoculated with an emulsion of the brain or spinal cord of a rabid dog. The medulla of this rabbit is again subdurally inoculated into other rabbits and by similar successive inoculations, the virus becomes active enough to kill all rabbits on the 6th to 7th day. This is called "*fixed virus*". For immunising a person bitten by a rabid animal the spinal cord containing this virus is attenuated by drying under caustic soda. Now 5% carbolised emulsion of the brain substance is used : 5 c.c. is the average dose, given subcutaneously daily (Semple's method). In very severe cases, the dose may be 10 c.c. and in mild cases, 2 c.c. For licks by a rabid animal, 7 and for bites, 14 injections are necessary.

Owing to a long incubation period of rabies, immunisation in the above way commencing soon after the infection is possible. The immunity produced by this is very dependable.

Locally, the wound surface immediately after the bite of the rabid animal should be cauterised with fuming nitric acid.

* *Annals of Internal Medicine*, October, 1935 ; also McKhann, Green and Coady, in *Jour. Pediat.*, vi. 6, 1935.

The virus used may be (a) attenuated, *living* fixed virus of Pasteur and Hogen : (b) carbolic or etherised vaccine having *killed* fixed virus : (c) 5% carbolic suspension of sheep brain infected with Paris virus (Semple).

COMPLICATIONS.—Itchy swelling at the site of injection and rarely paralytic phenomena (facial paralysis, dorsolumbar myelitis and Landry's paralysis) may appear.

(c) **BACTERIOPHAGE.**—This was believed to be a filter-passing lysin capable of dissolving or otherwise modifying bacterial activities.

Dysentery, cholera and mixed intestinal organisms group of bacteriophages were prepared and one ampoule dissolved in 20 c.c. vichy water was taken on empty stomach according to the urgency of the condition every 4 hours or in the morning and evening. As the results are not sufficiently dependable these are getting obsolete.

(d) **ANTIVENENE** or an antitoxic serum has been used for the treatment of snake-bite. The *Kasuali* variety is a mixed cobra and viper antivenene and prepared by graduated injections of the mixed toxin into a suitable horse.

The dose necessary depends on the amount of toxin injected in the bite and also on the rapidity of onset and the severity of the toxæmia. Usually an initial dose of 100 c.c. is injected intravenously which is repeated every two hours as required. Local and symptomatic treatments are also necessary.

Available in phials of 10 c.c., each c.c. neutralising 2 mg. of cobra toxin and 4 mg. of daboia toxin.

NON-SPECIFIC IMMUNE THERAPY

Immunisation by the specific bacterial substance either for prophylaxis or cure led to the speculation that the real antigen in these cases was the bacterial protein which was probably not strictly specific. The protein of bacteria other than that of infection especially when injected intravenously, causes a sharp rise of temperature and this itself in an infection like gonorrhœa leads to cure. In other cases the mechanism is more complicated. The following nonspecific agents are used for therapeutic purpose.—

(i) **T.A.B. vaccine** intravenously (see p. 729). **Old Tuberculin** (in minute doses in bronchial asthma). **Malaria therapy** (5 to 10 c.c. of the blood containing benign tertian parasites injected into a person suffering from general paralysis) and **Colloid sulphur** injections probably act by causing hyperpyrexia. (See p. 216).

(ii) **Milk protein.**—Sterilised protein, free from fat, 5 to 10 c.c. are administered intramuscularly in subacute arthritis, pelvic cellulitis and various septic processes acute or chronic. In 0.5 to 1 c.c. dose is sometimes given percutaneously also.

AOLAN, LACTOPROTEIN or LACTOLAN are usually used.

(iii) **Blood protein.**—The whole blood 5 to 10 c.c. or more from a healthy adult individual is injected intramuscularly twice a week either for passive immunity as in measles and anterior poliomyelitis or as a non-specific protein to cause immunity reaction in many infective processes, in bronchial asthma and in urticaria.

CONVALESCENT SERA have usefulness in certain varieties of virus infection. Otherwise intramuscular injection of a few c.c. whole blood for any direct immunity response is unjustifiable.

Whole blood may sometimes cause symptoms of allergy which may be alarming.

HEMOPROTEIN, a 10% solution of peptone derivatives of ox blood, in 0.1 c.c. or larger doses is given subcutaneously in many infective processes, also in asthma, urticaria and in chronic arthritis.

(iv) **Peptone.**—A 33% solution of Armour's dry peptone in glycerin and water, sterilized, 3 minims is the initial dose. Or to 30 c.c. of patient's blood serum is added 1.5 gm. of Armour No. 2, 0.006 gm. of agar and 10 drops of chloroform, sterilized and incubated at 37° to 40°C for 3 hours: 10 drops of the clear fluid obtained from it are given very slowly intravenously in bronchial asthma. The dose is cautiously increased. It is given intramuscularly in 5 to 7.5% solution and sometimes orally. This is now getting nearly obsolete.

(v) **Complex protein substances** as Omnadin, Sterodin or Polydin are also sometimes used, 1 to 2 c.c. intramuscularly and repeated twice a week.

CIBALBUMIN (an aqueous solution of animal protein) available in 2 c.c. ampoules is also used for non-specific immunisation: start with 1 c.c. subcutaneously.

BLOOD PROTEIN RESTORATION

Blood protein restoration may be required for a sudden blood loss, in shock and collapse, severe burn, in various conditions of hypoproteinæmia, severe infection and in certain hæmolytic conditions.

1. **THE WHOLE BLOOD.**—This is collected from a healthy donor who had no syphilis, no malaria and no jaundice within six months and hæmoglobin value was above 85%. The blood is collected and mixed with an anticoagulant in a bottle consisting of (a) 1.7 to 2% sodium acid citrate and 2.5% dextrose in water for injection: 120 ml. is adequate for 420 ml. of blood or (b) sodium citrate 1.6 g., citric acid 0.56 g. and dextrose 1.5 g. in 75 ml. of water for injection: this is ample for 500 ml. of blood. These solutions can be sterilised by autoclaving, delays hæmolysis of the red blood corpuscles after transfusion and blood in this solution can be used upto 21 days after collection. If 3% sodium citrate solution is used, the blood must be used immediately after collection.

During storage, the leucocytes disintegrate in a few hours, blood platelets disappear in 4 days and prothrombin, immune bodies and complement gradually disappear.

The blood hæmolysed shown by red colouration of the plasma above the corpuscular layer should not be used. The compatibility of the blood in the A, B, O and Rh systems must be carefully investigated before transfusion.

The transfusion restores the blood volume also the red blood corpuscles, platelets, clotting factors and other blood constituents which are deficient in the recipient.

2. PLASMA HUMANUM NORMALE CITRATUM (*Plas. Human. Norm. Cit.*), Citrated Normal Human Plasma. IND. PHARM. LIST.

Citrated Normal Human Plasma is the sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from 18 to 20 healthy persons. The cell free plasma is separated by centrifugation and stored at 4° to 6° for not less than 72 or more than 120 hours. At the end of the period clear supernatant plasma is pooled, all groups being mixed. Pooled plasma is sterilised by filtration and distributed in final containers through a closed system. It may be dispensed as liquid or dried plasma.

Dose, 20 fluid ounces or 500 ml.

3. SERUM HUMANUM NORMALE (*Serum Human. Norm.*), Normal Human Serum. IND. PHARM. LIST.

Normal Human Serum is the sterile serum obtained by pooling approximately equal amounts of the liquid portion of coagulated whole blood from 18 to 20 healthy people and sterilised by filtration. Collected blood in a closed system stored in sterile bottles, allowed to coagulate, centrifuged and kept at 4° to 5° for 72 to 120 hours. The cell free serum is pooled into sterile bottles and again sterilised by filtration and sterility test performed.

STORAGE.—Both these are preserved at a temperature between 2° to 10°. Fat and soaps may appear as a grey layer at the top: such serum may be used. Dried human serum must not be exposed to excessive heat. These are dispensed in unopened glass container.

Dose, 20 fluid ounce or 500 ml.

Transfusion of plasma is often an emergency measure before proper arrangement can be made for full blood transfusion. Plasma does not require any grouping and so it may be given intravenously from the stock. Usually one pint is given very slowly intravenously.

COMMERCIAL PRODUCT.—Normal Human Plasma, LYOVAC is obtained in bottles of 50 c.c. and 250 c.c. with 0.1% pyrogen free sterile citric acid solution. Preservatives is 1 in 25,00 phenyl mercuric borate.

DEXTRAN, 22 mg./kg. of body-weight has been used as plasma substitute: available as *Intradex* in 20 fl. oz. transfusion bottles.

4. Protein deficiency may also be restored by amino-acids in casein products.

CASEINUM SOLUBILE, soluble casein has casein with a small proportion of alkali. *Casein hydrolysate* is prepared by hydrolysing casein with alkalies, acids or enzymes and is a buff-coloured powder containing amino-acids, polypeptides and other breakdown products: amino-acids should be at least 60%. Enzyme hydrolysis causes least destruction of amino-acids.

Soluble casein is miscible with water and easily digested. It is useful in patient whose protein intake or digestion is

reduced or when excessive protein loss is going on. It may be given *by mouth* adequately flavoured or *intravenously* in aqueous solution of 2.5 to 10% of amino-acids with 3 to 10% of dextrose. The usual dose is 1 to 5/kg. of body-weight.

Casein hydrolysate may be used as bacteriological media, for feeding rats used in biological assays and for making non-greasy skin creams.

COMMERCIAL PREPARATIONS

BIOTOL, 20% amino-acid solution (16 oz. is given daily): CASEIN HYDROLYSATE (320 g. daily) and PROCASENOL, (protein carbohydrate granules) given orally.

AMINOXYL (enzymic casein hydrolysate, sodium chloride free), in powder, 1 to 2 g./kg. of body-weight daily in several divided doses every 3 to 4 hours is used.

AMINOZYME (amino-acids, vitamin B complex and C and digestive enzymes) liquid: daily dose, 1 fl. oz. or more.

CASINOL is soluble calcium (90% protein) is used in $\frac{1}{2}$ to one ounce doses or more daily.

CASEIONE (Casein Hydrolysate, proteolysed liver with Ca, Fe and vitamins A, B, C and D), in liquid form daily dose is $\frac{1}{2}$ to 1 fl. oz. or more.

HYDROPROTEIN, *oral* has 20% amino-acids, each fluid ounce representing 6 gm. of protein and available in 10 fl. oz. bottles: *injection* has 5% amino-acids in normal saline, available in 25 c.c. ampoules and 200 c.c. bottles.

ADDENDUM

1. CHLOROQUINE (p. 349) has alternative preparations of *Resochin* and *Nivaquine*.

2. ESTOPEN (hydriodide of diethylamine ethyl ester of penicillin G) and LEOCILLIN (benzyl penicillin-diethyl amino ethyl hydriodide) in 500,000 units vials once or twice daily are claimed to be more effective in lung infections.

3. VITAMIN B₁₂ (p. 298) for oral administration is tablet *Ucemine B₁₂*, each having 10 micrograms is growth-promoting in children. *Macrabin* "20" and *Macrabin* "50" have 20 and 50 microgram of vitamin B₁₂ used parenterally.

APPENDIX

A SYNOPSIS OF THE RULES FOR REGULATING POSSESSION FOR SALE AND THE SALE OF POISONS

(UNDER INDIAN POISONS ACT XII OF 1919)

1. The following restrictions shall apply to "wholesale" of poisons,—

(i) All receptacles containing the poison shall be securedly packed and bear the label "Poison", the name of the poison and the name and the address of the seller except when the manufacturer's name is present thereon.

(ii) In the case of a poison included in the Schedule I, a stock and sale register in the prescribed form shall be entered from day to day, provided no signature of purchasers shall be necessary and the sales may be posted in lots under a particular order according to the serial number of the transactions. All letters and written orders referred to the fifth column of the sale register shall be preserved in original where possible for a period of 2 years.

2. The following restrictions shall apply to the "retail sale" of poisons specified in Schedule II, namely,—

(i) Every vessel, package or covering containing such poison shall be labelled with (a) the name of the Poison, (b) the words "Poison" and "Not to be taken" "For External use only", distinctly printed both in English and the Vernacular in red letters and (c) the name and address of the vendor.

(ii) When any such poison is sold, it shall be securedly packed in a closed receptacle or packet and every such receptacle or packet shall be labelled by the vendor with a red label bearing the name of the poison in English and in the vernacular and the name and address of the vendor together with the date of sale, and

(iii) Every sale of such poison shall, as far as possible, be conducted by the licence-holder in person or where the licence-holder is a firm or company, through or under the supervision of an accredited representative of such firm or company.

(iv) Every licence-holder shall maintain a stock and a sale register in the prescribed form in which he shall enter the sales of poisons specified in the schedule. Separate pages shall be allotted in the register for each item of poison and the licence-holder shall enter thereon side by side all stock and sales of poisons. The register shall be totalled and balanced daily and

initialled by the licence-holder himself or by his accredited representative, if the licence-holder is a firm or a company. Provided that poisons issued from stock to the dispensary on any day, shall be entered as one item on the issue side of this register no detailed stock register being maintained of consumption in the dispensary.

(v) All such poisons which are kept for sale by the licence holder shall be kept in a box, almirah, room or building (according to the quantity maintained), secured by lock and key and in which no substance shall be kept other than poison possessed in accordance with a licence granted under the Act, and each of these poisons shall be kept within such box, almirah, room or building and receptacle shall be marked with the word "Poison" in red characters both in English and the vernacular, and in the case of receptacles kept for separate poisons, with the name of such poisons.

Provided that poisons issued for use in a chemist's dispensary need not be kept under lock and key after such issue during dispensing hours but should be kept in a separate shelf in the dispensary in bottles distinguishable by touch and colour from ordinary bottles.

3. The following further restrictions shall apply to the retail sale of poisons specified in Schedule I. namely,—

(i) A licence-holder shall not sell any such poison to any person unless he is personally known to him or is indentified to his satisfaction. He shall not sell any of the said poisons to any person who appears to him to be under the age of 18 years or to any person who does not appear to him to be in full possession of his faculties or to any wandering mendicant.

(ii) Before the delivery of such poisons an entry shall be made in the poison-register referred to in 2 (iv) above.

4. Every applicant for the renewal of licence shall make a written application to the District Magistrate or to the Sub-Divisional Officer and such application shall bear court-fee stamp of Rs. 2. Provided that in the case of persons holding excise licence, a poison licence may be granted for the sale of poisons covered by the excise licence on payment of a fee of Re. 1.

5. A licence shall terminate on the death of licence-holder or if granted to a firm or a company on the winding up or the transfer of the business of such firm or company.

6. The District Magistrate or the Sub-Divisional Officer may, for any sufficient cause, revoke or cancel any licence. Provided that an appeal shall lie from the District Magistrate to the Commissioner or from the Sub-Divisional Officer to the District Magistrate against an order cancelling or revoking a licence which has been granted or refusing to renew an existing licence.

7. Any Magistrate or Police officer or Medical or Health officer duly empowered in this respect by the District Magistrate or by the Commissioner of Police in Calcutta, may at any time visit and inspect the premises of a licence-holder, where any of the said poisons is kept for sale and may inspect the stock found therein and the registers maintained.

8. A licence-holder shall not sell powdered white arsenic to any person unless the same is, before the sale thereof, mixed with soot, indigo or Prussian blue in the proportion of at least half an ounce of soot, indigo or Prussian blue to one pound of white arsenic and so on in proportion for any greater or less quantity, provided that where the District Magistrate or the Sub-Divisional Officer is satisfied that such arsenic is required for some purpose for which such admixture would according to the representation of the vendor, render it unfit, the District Magistrate or Sub-Divisional Officer may authorise the vendor to sell without such admixture such quantity of white arsenic as he may think proper.

POISONOUS ARTICLES, SCHEDULE I

(Enforced from 1st April, 1932)

1. Aconite, Aconitine, Liniment and tincture of Aconite.
2. Arsenic metal, White Arsenic (Arsenious Oxide), Yellow Arsenic (Arsenic sulphite), Red Arsenic (Realgar), Copper Arsenite (Scheele's green), Copper aceto-arsenite (Paris green), Liquor Arsenicalis, Liquor Arsenic Hydrochloride, Arsenic chloride and bromide.
3. Atropine, Atropine Sulphate, Liquor Atropine Sulphate and other salts and preparations of atropine.
4. Barium sulphide.
5. Belladonna root, Belladonna leaves, Extract and Liquid Extract of Belladonna, Liniment of Belladonna.
6. Cannabis Indica, Extract of Cannabis Indica.
7. Cocaine, Cocaine Hydrochloride, and other salts and derivatives of cocaine both synthetic and natural, except such as are exempted under the Excise Act.
8. Corrosive Sublimate (Mercuric Chloride).
9. Cyanide of Potassium, Cyanide of Sodium, Acid Hydrocyanic (Prussic acid), concentrated and diluted.
10. Datura Leaves, Datura Seeds (Stramonium).
11. Morphine, Morphine and liquor morphine hydrochloride, Morphine and liquor morphine acetate, Heroin, Heroin Hydrochloride and other salts and derivatives of morphine.
12. Nux Vomica Seeds, Solid Extract of Nux Vomica, Liquid Extract of Nux Vomica, Tincture of Nux Vomica.
13. Opium, Tincture of Opium, Extract of Opium Solid, Extract of Opium Liquid, Liquor Opii Sedavitus.
14. Yellow Phosphorus.
15. Picrotoxin.
16. Savin oil.
17. Strychnine, Strychnine Nitrate, Strychnine Sulphate, Strychnine Hydrochloride, Liquor Strychnine Hydrochloride and all other salts and solutions and preparations containing 0.2% or more of strychnine.

SCHEDULE II

1. Antimony compounds, both organic and inorganic.
2. All organic compounds of Arsenic and all other inorganic compounds of Arsenic except those mentioned in Schedule I.
3. Barium Nitrate, Barium Chloride.
4. Cantharides, Tincture of Cantharides. Cantharidine.
5. Carbolic Acid containing not less than 3% of phenol.
6. Chloral hydrate.
7. Digitalis Leaves, Tincture of Digitalis, Digitalin.
8. Hyoscyamus (Henbane or *Khorasani Ajwan*) leaves, Ext. Hyoscyamus Liquid, Tincture of Hyoscyamus, Liquor Hyoscyamine Sulphate, Hyoscine Hydrobromide.
9. Mercury oxides (red, yellow or black), Ammoniated Mercury, Mercury sulphocyanide, Mercury iodide. Liquor Hydrarg. Perchloride.
10. Nitric Acid concentrated.
11. Oxalic Acid, Sodium oxalate, Potassium oxalate, Ammonium oxalate.
12. Red phosphorus, Rat poison containing red phosphorus.
13. Strophanthus, strophanthin, Extract Strophanthus Liquid. Tincture of Strophanthus.
14. Tincture of Belladonna.
15. Chloroform.

Stock and Sale Register

Name of the Firm.....

Address.....

NAME OF THE POISON

SALE.

STOCK.

[illegible]

INVALID FOOD RECIPES

I. Carbohydrate Preparations

(1) **BARLEY WATER.**—Take 2 oz. of pearl barley washed well in cold water or 3 heaped tea-spoonful of barely powder. Put it up in a saucepan with 1 pint of water and allow to simmer for 15 to 20 minutes. Strain, sweeten with sugar, flavour with a few drops of lemon juice and serve. If a thicker stuff is required, boiling is continued for about an hour or more.

A gruel is also made in the same way with arrowroot powder which is believed to be even lighter and better tolerated.

(2) **CHIRA (*Chura*) GRUEL.**—A heaped table-spoonful of fresh *chura* (pounded rice), well washed in cold water, is made to simmer in a saucepan with a pint of water for 20 to 25 minutes and strained. It is now flavoured as desired and served.

It is more easily digestible, contains the rice vitamins, has a better taste than barley water and better tolerated in bowel diseases.

(3) **SAGO AND OATMEAL GRUEL.**—A table-spoonful of fine sago or oat, well washed with several changes of cold water, is put into a saucepan with a pint of water and made to simmer for $\frac{1}{2}$ hour. This is strained and served, flavoured as desired.

This is a thicker preparation than the previous ones.

(4) **RICE GRUEL.**—A heaped table-spoonful of fine and well seasoned old rice is first washed with 3 or 4 changes of water and then boiled in a saucepan with one pint of water for 1 to $1\frac{1}{2}$ hour. This is strained and the gruel so formed is served, properly flavoured.

If a thicker stuff is required, the whole thing is made into a paste by rubbing down with the back of the spoon and strained through muslin. This may be taken with milk, fish or meat broth.

Machine-spread oats are available (Quacker Oats) which are mixed with water and boiled.

This is suitable for convalescent typhoid patients, before any solid food is given.

(5) **SOOJI GRUEL.**—One table-spoonful of *sooji* is added to $\frac{1}{2}$ to 1 pint of water and is made to simmer in a saucepan till made into a rather thick gruel. It is now served with sugar and lemon juice, milk, fish or meat broth.

II. Milk Preparations

(6) **LIME WHEY.**—Put $\frac{1}{2}$ pint of fresh milk in a saucepan add 4 oz. of water and boil. When it is bubbling, add sour

lime juice drop by drop till the milk cracks. Strain to separate the curds and the light green nearly *transparent* fluid so formed is the whey.

Whey is also prepared with calcium lactate, about 30 grains being required for $\frac{1}{2}$ pint of boiling milk.

If the whey is yet milky, the curds have only been partially separated and if sour to taste, this is due to adding too much of lime juice.

(7) **RENNET WHEY.**—To lukewarm boiled milk, the necessary amount of the essence of rennet is added according to the printed direction on the bottle and set aside in a warm place for the curds to separate.

Acid lime juice separates the curds best and lime whey is therefore most popular. Whey may be prepared with alum also but is not to be recommended on account of its astringent action.

(8) **POWDERED MILK FOOD.**—Plain milk powdered (as *Lactogen*, *Glaxo*, *Allenbury* No. 1 and *Vita milk*) or the same mixed with malt (as *Nestle's*, *Horlick's* malted milk, *Allenbury* No. 2, *Milo Food*), is prepared by first making a paste of the powder with cold water in an enamel or porcelain cup and then slowly adding hot water and thoroughly mixing with a spoon. The quantity of the powder required depends on the thickness of the preparation desired.

Defatted milk powder is available as *cowlac* or *butter milk powder* and is suitable in jaundice and fatty diarrhoea.

Acid milk as *Elidon* has advocates in infantile diarrhoea.

Also see *Lactic Acid Milk*, p. 261.

(9) **POWDERED FOOD, PREPARED WITH MILK.**—*Mellin's food* (malted carbohydrate), *Allenbury's* Malted food (mixture of wheat flour and malt), *Sanatogen*, *Sanaphos*, *Sanagen* or *Visem* (all containing casein glycerophosphate), is prepared by making a paste of the powder with cold water and then slowly adding hot milk. One or two tea-spoonfuls are usually required for a cup of hot milk.

Ovaltine (a special variety of cocoa containing malt and milk powder) and *Vitavose* (containing vitamin B, maltose and dextrin) are also prepared in the same way

Dextrimaltose or *Maltodextrin* contains easily assimilable carbohydrate as dextrose and maltose and is given with milk for increasing the nutrition value.

Casec (calcium caseinate) is the fat and sugar free milk curds in powdered form : especially indicated to increase protein intake, lessen intestinal acid fermentation and supply calcium.

For a breastfed infant, 2 packed level tea-spoonful and for a bottlefed one, 3 to 4 packed level table-spoonful may be given daily.

Sprulac has more protein and less fat and carbohydrate and is prescribed in sprue.

(10) PEPTONISING MILK.—(See p. 260).

Peptonised milk is easily assimilated and very useful in many conditions of weak digestion.

(11) JUNKET.—Take lukewarm milk, add sugar to it, put into a deep enamel dish and add essence of rennet or rennet powder in quantity indicated on the label of the container. Keep it undisturbed in a warm place or on warm water bath for 1 to 1½ hours when it sets. Add the required quantity of sugar and serve.

It is an easily digestible and palatable milk food and prescribed during convalescence.

(12) DAI.—This may be prepared in the same way. Instead of rennet, two tea-spoonfuls of good *dai* from the bazar are added to a pint of lukewarm milk and put up in warm water bath or in hot air chamber till it sets which usually takes three to four hours. If kept too long, it turns acid. It is a palatable and easily digestible milk food.

(13) OATMEAL PORRIDGE.—To two table-spoonfuls of oatmeal is added one pint of boiling water and a pinch of salt and slowly cooked, stirring briskly with a wooden spoon to avoid sticking at the bottom of the pan. This is continued for 20 to 40 minutes till it is sufficiently thick. It may be cooked with milk and sugar or these may be added afterwards.

(14) SOOJI PORRIDGE.—It is prepared in much the same way, milk and sugar being added when the *sooji* is partly boiled.

Sooji is sometimes fried in *ghee* and water or milk and sugar are then added. This is called *halowa* and is a good convalescent food.

(15) TYPHOID BREAD.—Take the inside soft pulp of the bread and put it into boiling milk. Make the whole thing into a paste by rubbing down with the back of a spoon. This is strained through fine muslin, sweetened with sugar and served.

This is a favourite semisolid food, suitable during the early stage of typhoid convalescence.

III. Egg Preparations

(16) ALBUMEN WATER.—Pour into a cup the white of a fresh egg, beat it thoroughly with a spoon and then slowly add water to make 3 fl. oz. Serve it with a pinch of salt, a little sugar and a few drops of orange flower water.

(17) EGG FLIP.—Beat 1 to 2 fresh eggs in a cup till made pasty and then slowly add 8 oz. of warm milk and 1 to 2 tea-spoonfuls of good brandy. Sweeten as required and serve.

(18) EGG POACH.—Boil a little water in a deep frying pan and add salt to taste. Break the egg in a cup, taking care to

keep the yellow entire. The pan is then taken out of the fire and the egg is gently slipped into it. Tilt the pan and with a spoon, gently fold the white on the yolk to give a round appearance and simmer till the white is set.

It may be flavoured by adding to the water a tea-spoonful of vinegar or a few drops of lemon juice.

(19) CUSTARD.—Beat up 2 eggs, add $\frac{1}{2}$ pint of milk, sweeten and flavour to taste. The preparation is now baked in a pie-dish or steamed in a basin.

IV. Broths and Soups

(20) VEGETABLE BROTH.—Unripe banana sliced, fig, brinjal tomato, *palval* and spinach all minced $\frac{1}{2}$ seer and *sona moong dal* two heaped up tea-spoonfuls are slowly boiled in a saucepan with one pint of water till reduced to half: strained and a pinch of salt and a few drops of lemon juice are added.

(21) VEGETABLE BROTH, FLAVOURED.—Carrot, peas, beans, cauliflower, cabbage, lettuce, lady's finger and potatoe are taken, making in all about $\frac{1}{2}$ seers, washed clean and minced. Into a pan on stove, add 2 to 3 tea-spoonfuls of cooking oil or butter and when this is "ripe", put the vegetables into it, mix well and allow to simmer. When these change colour, add one pint of water, required quantity of salt, pepper and turmeric, cover up well and allow to boil on slow fire. When the vegetables are softened, these are smashed with the back of the spoon and boiling is continued till the water is reduced to half. It is now strained through a piece of clean muslin and served.

The broth may be thickened by adding some pearl barley along with the vegetables at the time of boiling.

(22) DAL SOUP, PEA SOUP.—Into the saucepan on the stove 2 tea-spoonfuls of butter or cooking oil are put and when ready, one red chilli is thrown into it. As it changes colour, one table-spoonful of dal (*sona moong* or *musur*) or the same quantity of shelled peas is added and mixed well. It is stirred briskly for 5 minutes and then a pint of water added and well covered. It is allowed to simmer for 1 to $1\frac{1}{2}$ hour and flavoured with pepper, turmeric and salt. It is then strained through a clean piece of muslin to remove all solids and fat and served.

(23) FISH BROTH.—A live lean fish like a good sized *kai* or *singi* fish is taken. This is cut into small pieces and washed well in water.

Into a hot saucepan is put 2 tea-spoonfuls of cooking oil and when it is ready, a few slices of onion are thrown in and fried. The fish is then added also the required quantities of salt, pepper and turmeric. All these are well mixed and allowed to simmer till softened. One pint of water is then added, the pan is well closed and allowed to simmer on slow fire for about

$\frac{1}{2}$ to 1 hour. It is then strained through a clean piece of linen, the liquid juice being squeezed out of the fish and the solids and fat removed.

(24) CHICKEN or MUTTON BROTH.—Take one small chicken or half a pound of lean mutton from the neck free from fat. Mince it well including the bones. Place the meat and one quart of cold water in the saucepan and slowly boil. Continue for an hour and add if desired, some pearl barley, minced green vegetables, onion and flavourings as salt, ginger and pepper. Simmer gently for 2 hours, strain well so as to remove the solids and fat and serve.

(25) BEEF TEA.—Remove fat and mince the meat thoroughly. Place it in an earthenware jar, add sufficient quantity of water and salt and close it down. Place the jar in a saucepan of boiling water or in a slow oven and cook for 3 hours stirring occasionally. Strain, remove all traces of grease and serve. It may be flavoured either with lemon juice or cinnamon.

The same may be prepared with lean mutton for non-beef-eating patients.

(26) ESSENCE OF CHICKEN, (*Jug Soup*).—The meat from one chicken is taken ; it is finely minced including the bones. Into a fire-proof earthenware jar, first the bones and then the meat are put. The necessary amount of salt, a few slices of ginger and onion, a few bits of cinnamon bark and a little water are also added. The lid of the jar is now clamped almost airtight. It is then put into water in a saucepan and gently boiled for nearly 3 hours. When so cooked, the fluid is pressed out of the meat, strained with a piece of fine silk or filter paper to remove all grease and served.

(27) LIVER BROTH.—Take $\frac{1}{2}$ lb. of fresh goat's liver, wash well and mince. Put it into a buttered saucepan : allow it to simmer on slow fire, stir frequently till it just changes colour. Put a little salt, a pinch of turmeric and pepper and add one pint of water. Allow it to simmer for $1\frac{1}{2}$ to 2 hours. Squeeze the whole juice out, strain and serve.

(28) RAW MEAT JUICE.—Finely mince $\frac{1}{2}$ lb. of lean mutton, put it in a saucepan and add 4 oz. of potable cold water. Allow it to stand in a cool place for an hour and then press the juice out either with a pressing machine or by squeezing through a clean piece of linen.

One or two ounces of it are to be taken at a time flavoured, if necessary, with a few drops of lemon juice and a little pepper and salt.

(29) PATENT MEAT EXTRACTS.—*Bovril* (beef extract and finely powdered beef fibrin and albumen), Brand's *Meat Essences*, Valentine's *Meat juice*, *Panopeptone* (beef extract with wheat) are sometimes substituted for fresh meat extract. These are served by adding $\frac{1}{2}$ to 1 fl. oz. of the extract to a tea-cupful

of lukewarm water and if necessary flavoured with a few drops of lemon juice.

VIROL is a bone marrow preparation with egg, malt and lime : useful for poorly-nourished children.

These do not keep well in hot climate especially when the container is kept open for a few days. So these should better be not taken in the summer months.

Locally made *extract of chicken* have been put up in ampoules, one of which may be taken at a time. This is a more convenient and safe method.

CALORIFIC VALUE OF VARIOUS FOOD-STUFF

A normal diet contains a sufficient quantity of each of carbohydrate, fat, protein, vitamins, salts and water. The first two are mainly required to supply heat and energy for muscular work. The carbohydrates do this more readily and the diet must contain a preponderance of it. The protein is essential to replace the tissue wear and tear and also to supply some heat. The total daily protein requirement amounts to about 1 gram. per kilo body weight.

The heat unit or a *large calorie* is that amount of heat which is required to raise the temperature of one kilogram of water from 15° to 16°C. One gramme of each of carbohydrate, protein and fat oxidised in the body produces 4·1, 4·1 and 9·3 large calories respectively. One gram. of ethyl alcohol yields 7·7 calories. For basal metabolism of a human being of average built, about 10 to 12 calories per pound body weight are necessary and more for active work. An average adult weighing about 150 lbs. and doing a moderately hard work, requires a little over 3,000 calories and his normal diet should consist of 90 to 100 gram. of protein, 80 to 100 gram. fat and about 450 gram. of carbohydrate. The adjoining table shows the approximate composition of 1 oz. of various food-stuff in gramme.

1. VEGETABLES UP TO 5% CARBOHYDRATE CONTENT

| 28·3 gm. (1 oz.) | Carbohydrate. | Protein. | Fat. |
|--------------------------------|---------------|----------|-------|
| <i>Barbati</i> | ... 0·6 | 1·0 | 0·6 |
| Black-berry (<i>Kalajam</i>) | ... 1·02 | 0·4 | 0·03 |
| Brinjal | ... 1·4 | 0·2 | 0·09 |
| Cabbage | ... 1·2 | 0·4 | 0·03 |
| <i>Chaulkumra</i> | ... 0·4 | 0·45 | 0·08 |
| <i>Chichinga</i> | ... 0·4 | 0·1 | trace |
| Cucumber | ... 0·57 | 0·17 | 0·02 |
| French bean | ... 1·2 | 0·8 | 0·3 |
| Gourd (<i>Kaddu</i>) | ... 0·2 | 0·1 | 0·7 |
| <i>Jhinga</i> | ... 0·14 | 0·07 | 0·02 |
| <i>Karela</i> | ... 0·2 | 0·16 | 0·1 |
| Lettuce | ... 0·4 | 0·4 | 0·3 |
| Melon (<i>footee</i>) | ... 1·1 | 0·4 | — |

| 28.3 gm. (1 oz.) | Carbohydrate. | Protein. | Fat. |
|----------------------------------|---------------|----------|-------|
| <i>Mocha</i> | ... 0.7 | 0.02 | — |
| <i>Palbal</i> | ... 0.36 | 0.22 | 0.02 |
| Papaya | ... 0.1 | 0.16 | 0.01 |
| Peaches | ... 1.2 | 0.18 | 0.01 |
| Pomegranate | ... 0.2 | 0.18 | — |
| Pumpkin (<i>belati koomra</i>) | ... 1.47 | 0.3 | 0.03 |
| <i>Puin Sak</i> | ... 0.1 | trace | trace |
| Radishes | ... 0.96 | 0.28 | 0.03 |
| Rose-berry (<i>Golapjam</i>) | ... 1.4 | 0.4 | 0.01 |
| Spinach (<i>Palong Sak</i>) | ... 0.8 | 0.4 | 0.01 |
| Tomato | ... 1.2 | 0.2 | 0.12 |
| Turnip | ... 1.25 | 0.4 | 0.06 |

2. VEGETABLES OF 5 to 10% CARBOHYDRATE CONTENT

| | | | |
|--------------------------------|---------|------|------|
| Almonds | ... 2.1 | 6.7 | 15.1 |
| Apple | ... 2.2 | 0.1 | 0.06 |
| Beans | ... 2.1 | 0.37 | 0.17 |
| <i>Bedana</i> | ... 2.2 | 0.3 | — |
| Carrot | ... 2.0 | 0.2 | 0.03 |
| Cauliflower | ... 1.6 | 0.5 | 0.06 |
| Lady's Finger (<i>Vindi</i>) | ... 1.6 | 0.5 | 0.3 |
| Lichee | ... 1.8 | 0.9 | 0.06 |
| Musk melon (<i>Kharbuja</i>) | ... 1.9 | 0.6 | — |
| Onion | ... 2.5 | 0.35 | 0.8 |
| Orange | ... 2.4 | 0.2 | 0.1 |
| Pears | ... 2.3 | 0.1 | 0.03 |
| Pineapple | ... 2.2 | 0.16 | 0.09 |
| Water melon | ... 1.8 | 0.2 | 0.1 |

3. VEGETABLES OF 10 to 20% CARBOHYDRATE CONTENT

| | | | |
|------------------------------|---------|------|------|
| <i>Bael</i> | ... 4.5 | 0.19 | 0.2 |
| Beet | ... 3.2 | 0.5 | 0.6 |
| Green peas | ... 3.4 | 1.8 | 0.15 |
| Green plantain | ... 4.8 | 0.5 | 0.8 |
| Guava | ... 3.3 | 0.1 | 0.2 |
| Jack fruit (green) | ... 4.5 | 2.5 | 0.3 |
| Knol Khol (<i>Ol Kobi</i>) | ... 3.3 | 0.26 | 0.16 |
| Mango (ripe) | ... 5.1 | 0.5 | 1.1 |
| <i>Mankachu</i> | ... 3.3 | 0.6 | 0.4 |
| <i>Ole</i> | ... 3.6 | 0.6 | 0.9 |
| Pistachios (<i>Pesta</i>) | ... 4.7 | 6.5 | 16.3 |
| Plantain | ... 4.1 | 0.5 | — |
| Plum | ... 4.1 | 0.03 | — |
| Walnut | ... 4.8 | 4.9 | 18.9 |

4. VEGETABLES OF 20 to 30% CARBOHYDRATE CONTENT

| | | | |
|-------------------------------|---------|------|------|
| Grapes | ... 6.7 | 0.16 | — |
| Jack fruit (ripe) | ... 5.2 | 0.3 | 0.12 |
| Potato (boiled) | ... 5.7 | 0.5 | 0.1 |
| <i>Ranga-alu</i> | ... 5.9 | 0.2 | 0.8 |
| Water-nut (<i>Paniphal</i>) | ... 5.7 | 0.3 | — |

5. VEGETABLES OF HIGHER CARBOHYDRATE CONTENT

| 28·3 gm. (1 oz.) | Carbohydrate. | Protein. | Fat. |
|----------------------------|---------------|----------|------|
| Apricot (<i>Khobani</i>) | 14 | 1·6 | 0·09 |
| Cocoanut | 7·9 | 1·6 | 14·3 |
| Date | 19·7 | 0·4 | 0·03 |
| Garlic | 7·9 | 1·9 | 0·03 |
| Ground nut | 6·9 | 7·3 | 10·9 |
| Jack fruit seeds | 8·7 | 3·6 | 0·8 |
| Potato | 8·15 | 0·7 | 0·04 |
| Raisins | 21·6 | 0·7 | 0·9 |
| Tamarind | 8·9 | 0·4 | — |

CEREALS AND LENTILS

| | | | |
|------------------------|------|------|------|
| Arrowroot | 23·6 | 0·23 | — |
| <i>Atta</i> | 19·2 | 3·9 | 0·6 |
| Barley | 20·2 | 2·9 | 0·7 |
| Bread (brown) | 13·8 | 2·6 | 0·26 |
| Bread (white) | 14·8 | 2·7 | 0·35 |
| <i>Chhola</i> (entire) | 16·7 | 6·3 | 1·3 |
| <i>Chura</i> | 21·2 | 1·7 | 0·03 |
| <i>Dal</i> (average) | 16 | 6·8 | 0·97 |
| <i>Khoi</i> | 20·8 | 1·9 | 0·7 |
| Macaroni | 20 | 3·9 | 0·26 |
| <i>Maida</i> | 21·6 | 3·1 | 0·3 |
| Maize | 20·8 | 2·1 | 0·48 |
| Oatmeal | 19·8 | 3·4 | 2·4 |
| Rice (perboiled) | 25·5 | 1·8 | 0·2 |
| Rice (polished) | 26 | 1·8 | 0·13 |
| Rice (unpolished) | 22·2 | 2·3 | 0·04 |
| Sago | 22 | 2·1 | — |
| Sooji | 14 | 4·0 | 0·6 |
| Soya bean | 9·5 | 9·6 | 4·7 |

MILK AND MILK PRODUCTS

| | | | |
|--------------------------|------|-----|-------|
| Butter | 0 | 0·3 | 24·7 |
| Casein (<i>Chhana</i>) | 0·1 | 6·3 | 5·2 |
| Cheese | 0·8 | 7·5 | 9·4 |
| Cream | 1·2 | 0·7 | 5·8 |
| Curd (<i>Dahi</i>) | 0·78 | 1·3 | 1 |
| Ghee | 0 | 0 | 24 |
| Milk (Buffalo) | 1·4 | 1·2 | 2·5 |
| Milk (Cow) | 1·3 | 1·2 | 1·2 |
| Milk (Goat) | 1·1 | 1·2 | 1·2 |
| Milk (Human) | 1 | 0·5 | 1·5 |
| Skimmed Milk | 1·5 | 0·9 | 0·8 |
| Whey | 1·4 | 0·3 | trace |

FISH, MEAT AND EGG

| | | | |
|----------------|------|-----|-----|
| Beef (lean) | 0 | 6·2 | 2·1 |
| Chicken | 0 | 6·5 | 0·4 |
| Duck | 0 | 5·8 | 3 |
| Egg (Duck's) | 0 | 3·8 | 4·1 |
| Egg (Hen's) | 0 | 3·8 | 3·3 |
| Fish (average) | 0 | 5·4 | 1·1 |
| Goat's meat | 0 | 6·8 | 0·7 |
| Liver | 0·8 | 6 | 1·7 |
| Mutton | 0 | 3·8 | 9·4 |
| Pigeon | 0 | 6 | 1·9 |
| Prawn | 0·02 | 4·8 | 0·1 |

FATS AND OILS

| 28.3 gm. (1 oz.) | Carbohydrate. | Protein. | Fat. |
|------------------|---------------|----------|------|
| Cod-liver oil | ... | 0 | 28.0 |
| Cocoanut oil | ... | 0 | 28.2 |
| Lard | ... | 0 | 28.4 |
| Mustard oil | ... | 0 | 28.2 |
| Olive oil | ... | 0 | 28.3 |
| Ground nut oil | ... | 0 | 28.0 |

VITAMIN CONTENT OF FOOD-STUFF

| | A | B | C | D |
|----------------------|-----|---|---|---|
| Almond | ... | S | — | — |
| Apple | ... | M | M | — |
| Atta | ... | M | — | — |
| Banana | ... | S | S | — |
| Bean | ... | M | M | — |
| Beet | ... | S | S | — |
| Brain | ... | M | — | S |
| Butter | ... | — | — | S |
| Cabbage | ... | M | H | — |
| Carrot | ... | S | S | — |
| Cauliflower | ... | M | S | — |
| Cheese | ... | S | — | — |
| Cocoanut | ... | M | — | S |
| Cod-liver oil | ... | V | — | H |
| Cream | ... | M | S | S |
| Curd (<i>Dahi</i>) | ... | S | S | — |
| <i>Dal</i> | ... | M | — | — |
| Egg | ... | M | — | — |
| Fish | ... | M | — | M |
| Flour (white) | ... | V | — | — |
| Garlic | ... | S | M | — |
| Grape | ... | M | M | — |
| <i>Goor</i> | ... | ? | — | — |
| Kidney | ... | M | V | S |
| Lemon | ... | M | H | — |
| Lettuce | ... | M | H | — |
| Liver | ... | M | S | V |
| Maize | ... | M | — | — |
| Milk (Fresh) | ... | M | M | M |
| Mutton | ... | S | V | S |
| Onion | ... | M | M | — |
| Orange | ... | M | H | — |
| Peaches | ... | S | M | — |
| Peas | ... | M | H | S |
| Papaya | ... | S | M | — |
| Pineapple | ... | M | H | — |
| Potato | ... | M | M | — |
| Rice (unpolished) | ... | V | — | — |
| Rice (polished) | ... | — | — | — |
| Soya bean | ... | S | — | — |
| Spinach | ... | H | M | — |
| Sugar cane | ... | S | S | — |
| Tomato | ... | H | H | — |
| Wheat | ... | M | — | — |

H for high ; M for moderately high ; S for smaller proportion ;
V for variable ; — for nil or unknown.

RADIOTHERAPY

BY

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Fundamentally, the radiant energy is similar to each other, being electro-magnetic oscillations propagated through the space with a uniform velocity of 3×10^8 meters per second. They differ in their number of oscillations per second, i.e. in their wave length ; the quickly vibrating groups have proportionately shorter wave lengths than the slowly vibrating bands.

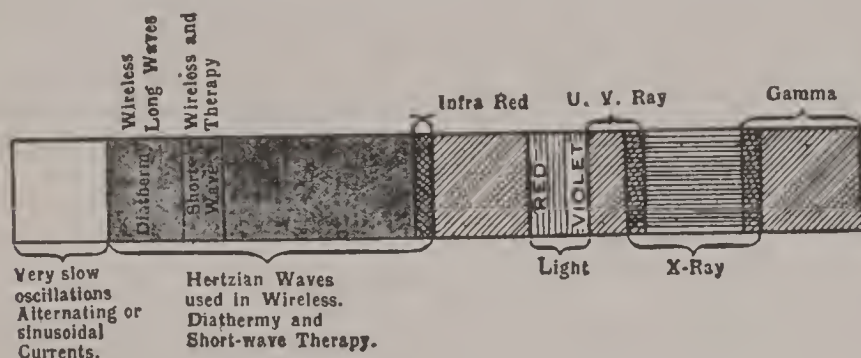


Fig. 62. The Electromagnetic Spectrum

If the various radiations are arranged according to their wave lengths, starting with the long ones on the left we obtain a diagram called the "electro-magnetic spectrum", from its similarity to the band of colours, when sunlight passes through a glass prism and falls on a screen or the wall behind.

X-RAYS AND RADIUM

These are considered together as their effects upon tissues, normal and pathological, are more or less the same.

(1) *X-Rays* are produced in high vacua tubes of special construction, when high voltage electrical current is passed through them. If the voltage is comparatively low, *soft*, i.e., less penetrating rays are produced, whereas if the voltage is high, *hard*, i.e., deeply penetrating rays are emitted.

(2) *Radium* is obtained by a complicated process of extraction from certain ores known as *pitch blende*.

Radium and its salts are continuously undergoing spontaneous atomic disintegrations ; electrically charged particles are ejected with great velocity from the nucleus of the atom.

The ejected particles or corpuscles, are either positively or negatively charged : the positives are *alpha*, and the negatives, *beta* rays. As a result of, and along with this corpuscular emission a vibration is set up in the ether, akin to light or X-rays of great rapidity. This vibration is *gamma ray*.

Radium owes its therapeutic value practically solely to the *gamma rays*. At present, experiments are being conducted to produce X-Rays of very high penetrating power, so that they may approach the gamma rays.

ACTION OF THE RAYS.—With certain reservations, the effects of X-Rays and gamma rays on the tissues are the same. Broadly speaking normal tissue is more resistant to irradiation than a pathological one. This is the fundamental basis of radiation therapy ; by a judicious dose of the rays, the pathological tissue is adversely affected whereas no harm is done to the surrounding normal tissues.

Sensitivity of the cells to irradiation depends on their reproductive capacity, mitotic activity and embryonicity. The more embryonic a tissue is, the more sensitive it is to radiation. A malignant tumour undergoing rapid cellular proliferation and thus resembling embryonic tissue, is easily destroyed by radiation.

X-Ray Treatment

This is given by projecting the rays from a certain distance on to the diseased part, interposing a sheet or sheets of aluminium, zinc or copper or even simple wash leather, called "*filters*" in the path of the rays, according to the special need. The filters cut off the less penetrating rays which would otherwise be absorbed in the superficial layers of the skin and thus cause a "burn" before a requisite amount of adequately harder rays could be delivered to the focus of disease deeper down.

Generally, for disease strictly localised to the skin and subcutaneous tissues a low voltage and a thin sheet of aluminium or a few layers of wash leather as filter are employed (*superficial therapy*). For diseases in tissues within a centimeter or so beneath the skin, e.g., tubercular cervical glands or cancer of the breast, a moderate voltage and a thick aluminium filter are used (*medium or semi-deep therapy*) ; whereas, for diseases in deep-seated internal organs as carcinoma of the prostate, a very much higher voltage and either copper or zinc filters are required, the so-called *deep-therapy*.

Chaoul's Therapy or low voltage contact therapy is only a modification of the technique of applying very soft rays generated in a special apparatus, at a close range to the diseased area, or a cavity in the body, e.g., mouth. It has a limited complementary value in radiation treatment of cancer. *Grenz-Kay Therapy* is yet another type of superficial radiation therapy : very soft rays are utilised.

Radium Therapy

Radium sulphate or carbonate in varying quantities (usually in milligrams) is enclosed in small platinum tubes, which are either blunt or pointed at one extremity with an eyelet at the other, called "needles". The platinum encasement serves as filter to cut off the alpha, beta and the soft gamma rays, allowing only the hard gamma rays to reach the tissues.

The tubes are placed in the natural cavities of the body as mouth, rectum, vagina or uterus as necessary. This is known as the *cavitary method*.

The needles after being threaded and sterilised are inserted into and around a new growth. This is called the *interstitial method* of application.

Sheets of metal of various sizes and shapes conforming to the contours of the different parts of the body, painted over with a special varnish in which is incorporated definite amounts of radium salts, are applied to the surface of the body. Now-a-days this method of *surface application* has been practically replaced by another method. The needles may be arranged on the surface of a cast made of a paste of paraffin, beeswax and saw dust (Columbia paste) and strapped on to the affected part for the requisite number hours.

Besides the above, there is yet another method of application, the so-called "*bomb*" method or *tele curie* therapy in which a large quantity of radium salt (4 gm. or more) enclosed in a suitable holder, is suspended over the part at some distance.

Radon Seeds.—The "seeds" consist of minute glass capillary tubes sealed at both ends containing the gas Randon or radium emanation and enclosed in gold or platinum sheaths. The seeds are fully active when freshly prepared, but they lose half their strength in 4 days and about 99·9% after 30 days, so that if not removed, only inert substances are ultimately left in the tissues.

THERAPEUTICS.—Good results have been obtained with radium in the treatment of the following diseases : ringworm, eczema, psoriasis, prurigo, barber's itch, lupus, chronic indolent ulcers, nævus, keloids, epithelioma of the skin and mucous membranes, malignant diseases of the internal organs, fibromyoma of the uterus, fibro-adenoma of the prostate, menorrhagias, monopause, exophthalmic goitre, leukæmias, pernicious anæmia, Hodgkin's disease, tubercular gland, peritoneum and bone diseases, intractable fibrositis, neuritis and arthritis.

It should be noted however, that X-Rays are usually used for all the above diseases and the application of Radium is more or less restricted to malignant diseases and a few of the benign conditions like nævus and keloid.

ULTRA-VIOLET RAYS

These waves occupy the portion of the electro-magnetic spectrum lying between the visible violet rays and the very soft X-Rays. The U.V. Rays are invisible. They are present in the radiations of all luminous bodies but the quantity available varies with the source.

The sun light, as obtained in high altitudes or in midocean, i.e., away from dust, damp and smoke, is rich in ultra violet rays but the intensity varies with the time of the day, the season of the year and atmospheric conditions even in the high altitudes. The sun is therefore an uncertain source. Hence to get a standard source, available at all times and of practically steady supply, the use is made of the mercury vapour arc, lit up inside a quartz burner by electrical current. There are other artificial sources also, e.g., the carbon and the tungsten arc lamps, but certain drawbacks are associated with their use. The mercury vapour lamp is now one of choice for therapeutic purposes. To get uniformly good results, the burner should be changed periodically, as after about 500 hours' service, an opacity develops inside the burner which prevents emission of the U.V. Rays.

LOCAL EFFECTS.—This is the production of an *erythema* after a latent period of 6 to 8 hours. The erythema may persist from 2 days to 2 weeks followed by minute scaly desquamation and bronzing of the skin. An *analgesic effect* is also produced in the painful areas.

GENERAL EFFECTS.—The chief are, (i) increase of calcium, phosphorus, iron and iodine contents of the blood ; (ii) increase of antigenic properties of blood ; (iii) stimulation of the endocrine glands ; (iv) activation of the cholesterol of the skin into vitamin D and (v) a feeling of buoyancy and general wellbeing.

The effects of an over-dose are, *locally* formation of blisters and *generally*, onset of irritability, insomnia, loss of appetite and of a feeling of prostration. There is however no permanent ill effect.

THERAPEUTICS.—The number of maladies in which the U.V. Rays are used, is legion with good, bad and indifferent results. As a general guide, it may be mentioned that good results have been obtained in the following.—Rickets, marasmus, post-febrile debility, anæmia, surgical tuberculosis, certain skin diseases, e.g., lupus, acne, carbuncle, erysipelas, weeping eczema, alopecia areata etc.

INFRA-RED RAYS

The usual source of these for therapeutic purposes consists of a high candle-power glass electric light bulb partially filled with nitrogen and mounted on a suitable stand with a reflector.

The radiations consist of a mixture of the visible luminous rays and more of the invisible infra-red or heat rays.

ACTION.—Infra-red radiation is absorbed in the sub-epidermal capillaries, the superficial muscles and fascial planes, causing local vasodilatation and erythema within about 10 minutes relieving congestion of the deeper parts. Other general effects are stimulation of metabolism, moderate increase of the red blood corpuscles and diminution of the whites.

THERAPEUTICS.—The rays are applied locally with good results in fibrositis, neuralgia, neuritis, myositis, muscular wasting, rheumatoid and gouty arthritis, abscess, whitlows, dry pleurisy, early pyorrhœa alveolaris and in leukæmias with encouraging results.

DIATHERMY

The use is made of alternating current of a very high number of alternations (one million and over) per second generated by means of a special apparatus. These currents also belong to the electro-magnetic spectrum and are akin to the wireless waves.

These high frequency currents do not excite the muscles and nerves. It is possible, by means of suitable connections, to pass a fairly large amount of this current through the body. Heat is generated in the tissue lying in the path of the current because of electrical resistance.

ACTION.—*Locally*, active hyperæmia is induced: the blood vessels dilate: viscosity of the blood is reduced and hence the circulation of the part is accelerated. If the intensity of the current is very great, heat produced coagulates the tissues to varying depths: tissues may be cut through as by a knife with the production of a thin filmy coagulum on the cut surfaces, preventing vascular oozing. This is known as the "high frequency cut". This has been found possible with malignant tumour, piles or tonsils.

GENERAL EFFECTS are produced only if a large mass of tissue is subjected to diathermy, as by placing electrodes to the front and back of the trunk. The effects are lowering of the blood pressure, increase of the pulse rate and increase of the metabolic rate followed by a diminution.

Diathermy relieves pain and spasm, removes congestion, helps the tissues in the resolution of inflammation and exerts a direct or indirect bactericidal effect or lowering the virulence of the invading organisms.

Diathermy has been used in gonorrhœal complications, rheumatoid arthritis, neuritis, neuralgias, lobar pneumonia, angina pectoris, chronic colitis etc.

SHORT WAVE THERAPY

The "short wave therapy" in contra-distinction to "diathermo-therapy", has the wave length of near about 10 meters whereas in the latter, it is about 500 meters and upwards.

The requisite wave length is obtained by placing the part requiring treatment in a condenser field between two applicators connected to an apparatus which utilises the "closed oscillatory circuit."

EFFECTS OF SHORT WAVES.—These are (i) Rise of *temperature* of the tissues included between the applicators. Heat can be produced at a greater depth and also can, to a great extent, be more selectively localised in certain tissues.

(ii) Changes in the viscosity, colloidal stability and chemistry of *blood serum*.

(iii) Rise of *phagocytic index* of blood takes place with moderate doses but with a heavy dose the index falls.

(iv) Direct *lethal effect on many bacteria* have been noted independent of the heat produced.

THERAPEUTICS.—Practically all conditions where diathermo-therapy is indicated are more quickly and more effectively influenced by short-wave therapy. Satisfactory results have been reported in the treatment of lung abscess, empyema and suppurative sinusitis.

INDEX OF MEDICAL TREATMENT

f. = Prescription. p. = Page.

Abortion, threatened.—Rest in bed. Morphine gr. $\frac{1}{4}$ hypoderm. also f. 499. If big clots are passed consult an obstetrician. *Prophylactic*, progesterone, p. 397 and vitamin E, p. 287.

Abscess of the Liver.—Emetine p. 352, 1 gr. hypodermically and orally chloroquine, p. 349 and 736. Also for intestinal amœbiasis kurchi alkaloids, p. 354 and chiniofon, p. 355 and enterovioform and others, p. 356 orally. Locally, kaolin poultice, p. 140.

Abscess Superficial.—*Locally* kaolin poultice, p. 140 ; *orally* sulphonamide, p. 366 ; *intramuscularly* and locally penicillin, p. 375 and hypodermically, strepto.-staphylo. vaccine. If much inflammation, f. 127. ; also see p. 176.

Acetonæmia.—Investigate the cause. Open out the bowels by an enema or f. 131, 225 and 393 ; glucose, p. 107 ; insulin, p. 414 : also see Acidosis.

Acidity.—Treat the cause. Orally, f. 55, 171, 194, 232, 234. Mag. oxide and trisilicate, p. 213 ; milk of magnesia, bisurated magnesia, tribasic mag. phos., p. 214. Kaolin, p. 140 : aluminium hydroxide, p. 141 : Antacids, p. 688.

Acidity of Fermentation.—f. 118, 119, 180, 181 : takadiastase, papain, lactopeptine, p. 201 ; sulphocarbolates, p. 169 ; lacteol, p. 263 : also see p. 691.

Acidosis.—Treat the cause. Orally, f. 126, 166, 173. Sod. lact., p. 255.

Acne.—*Locally*, f. 80, 135, 137 : also lotio alba, p. 436. Sulphathiazole, p. 366. Acne vaccine, p. 729. Attend to general health.

Adenitis.—Look for the cause and treat. For acute inflammation, f. 68 : for chronic, f. 67. Tuberculin, p. 723.

Addison's Disease.—Suprarenal cortical extract, see p. 387.

Agranulocytosis.—Remove the cause. Sodium pentose nucleotide, p. 263 : also folic acid, p. 297.

Allergy.—Investigate the cause and remove as far as possible. Desensitization, p. 673. Antihistamines, p. 673.

Alopecia.—Attend to the general health. - Thyroid gland, p. 407. Locally, f. 38, 40, 91, 418 and 419.

Amenorrhœa.—Gonadotropic preparations, p. 396. Also f. 144, 276 and 277.

Amœbiasis.—If *intestinal*, see Dysentery, p. 356 and f. 261 to 264. If *hepatic*, emetine, p. 352 and chloroquine, p. 349 and p. 736.

Anasarca.—Usually *renal* (see Nephritis) or *cardiac decompensation*. Rest in bed. Keep the body warm. Purgative, f. 123, 124, 149, 223 also pulv. jalap co. p. 227 : purgatives are not now-a-days as much used. If *cardiac*, digitalis, p. 654 ; f. 223, 366, 368, 369, 452, 487 and 489. Strophanthin, ouabain, p. 658 and squill, p. 660 : also anasarcin, scillaren and apocynum, p. 660, 661. *Diuretics*, f. 170, 176, 458. Caffeine group, p. 532. Mersalyl, p. 310 also novasurol, salyrgan, thiomerein, mercuhydrin, p. 313 and ammon. chloride p. 703. Hot air bath : pilocarpine p. 598 (now not much used). If *with anæmia* f. 280.

Anæmia (i) *Hyperchromic*.—For *tropical nutritional anæmia* and *sprue syndrome*, folic acid, p. 297, may be with whole liver extract, p. 419, is effective : for *pernicious (Addisonian) anæmia*, pure liver extract as anahæmin, p. 418 and vitamin B₁₂, p. 298 are needed. Iron preparations are needed in severe anæmia improving with the above treatment, p. 426. Other associated factors as bowels disorders, intestinal worms, hæmolytic strepto. infection should also receive attention. (ii) *Hypo-chromic* : treat the cause and give, f. 237, 239, 242, 271 to 280, 302 : vitamin C, p. 299. For *children with retarded growth*, vitamin B₁₂, p. 736.

Diet should contain a fair quantity of assimilable proteins and vitamins. Bowels are to be kept free.

Anæsthesia.—(a) *Local* : for conjunctiva, f. 405, 407 and for others, p. 577. (b) *Basal*, p. 443, 456, 479, 495 and 497. (c) *Obstetric*, p. 522, 551, 615.

Angina Pectoris.—Remove the exciting cause and enjoin more rest. During the attack give absolute rest and amyl nitrite, p. 667 also trinitrin, sodium nitrite, p. 668 and octyl nitrite, p. 669 : f. 467. *Sedatives* as bromide, chloral hydrate, f. 319, 328 ; morphine, f. 343 ; delaudid, eupaco, eukodal, p. 521 ; pethidine, p. 522 : amidone, p. 523 : benzyl benzoate, p. 679. *Coronary vaso-dilators* ; theophylline, euphylline and theominal, p. 532, 534 ; Pot. iod., p. 266. Lacarnol and padutin, p. 670 ; sulphocyanates, rhodan calc. diuretin and thiocyanate, p. 677. Also glucose with small doses of insulin, p. 416. Diathermy, p. 755.

Ancylostomiasis.—Tetrachlorethylene, p. 192. Oil of chenopodium, carbon tetrachloride, p. 191. Afterwards restoratives as f. 118 to 121 also f. 273 to 275 and 312.

Anthrax.—Penicillin, p. 370.

Apoplexy (cerebral hæmorrhage).—*Preventive* : attend to the arterial disease. (See Hypertension). *When in coma*, absolute rest preferably at the very spot, usually with the head up. Bowels are opened out, p. 211. Lumbar puncture is necessary ;

venesection is not now recommended. Cardiac stimulants, f. 397 also nikethamide and leptazol, p. 557 : oxygen, p. 558. Recovery is uncommon. *If recovered*, give prolonged rest in bed and treatment of arteriosclerotic condition.

Arthritis.—(See also acute rheumatic fever, gonorrhœa and gout). *Locally*, f. 6, 7, 16, 23, 67, 68, 211, 315, 326, 384 and 385. Also bee-venom, p. 136 : iodex and iodolep, p. 161 : entodon and iodeol, p. 161, iodine, f. 71 ; irgapyrin, p. 548 ; histamine, p. 672 ; milk protein, T.A.B. vaccine, p. 733 : yatren-casein, p. 356 : recently, A.C.T.H., p. 386. *Orally*, pot. iod., p. 265. *In strepto. viridis*, arthritis, sulphonamide, p. 364 : also vitamin C. *If rheumatoid*, gold, p. 441.

Ascariasis.—The worms are expelled by f. 113, 114 : two courses of treatment at the interval of two weeks may be needed.

Asthenia.—Investigate the cause : if it is neurosis or depressive state, amphetamine, p. 627 : drinalfa, p. 626 and dexedrine, p. 628. Ultra-violet rays, p. 754.

Asthma.—During fits, *inhalation* of amyl nitrite, p. 665 or fumes of stramonium, f. 441, 442. Also *spray*, adrenaline, p. 622 and ephedrine, f. 448. Inj. of adreno-ephedrine, evatmine, p. 626. *Orally*, f. 184, 188, 240, 363, 364, 370, 371, 435, 443, 444, 447, 476 and isopropyl preparations, p. 623. Look for the anaphylactic factor and also for any foci of focal sepsis especially oronasal ; autogenous vaccine esp. if the infective organisms are m. catarrhalis or pneumobacilli. Antihistamines, p. 673. Arsenic preparations as liq. arsenicalis, p. 320 or acetarsol, p. 324 parenterally are useful in cases with marked eosinophilia. Bowels are to be kept free. Over-eating and food that brings in an attack should be avoided.

Asthma, Cardiac.—*Prophylactic* : rest, restriction in diet especially in fluid and sodium chloride intake : an injection of mercurial diuretic, p. 313, once weekly : digitalis, p. 655 : theophylline-barbiturate, p. 539 at bed-time. *For the attack*, propping in bed, morphine gr. $\frac{1}{6}$ to $\frac{1}{4}$ hypodermically, p. 510 : sometimes adrenaline, venesection if much venous engorgement and intravenous digoxin, p. 655.

Auricular Fibrillation.—Rest in bed ; f. 452 and quinidine, p. 345 also mepacrine, p. 347. If due to hyperthyroidism or any other toxæmia, improvement is less marked till this is corrected.

Auricular Flutter.—Digitalis, p. 455 and quinidine, p. 345.

Bacilluria.—*B. Coli* : f. 108, 167, 168, 170 till urine is alkaline, also sulphonamides, p. 366 ; this is sufficient in most cases. If not, acidify with ammon. chlor., p. 703 and administer sodium, calcium or ammon. mandelate, p. 704. In some cases, acid sod. phosph., p. 702 and hexamine, p. 706 and occasionally caprokol, p. 172, neotropin, p. 177, autogenous vaccine. Recently

streptomycin, p. 377 and chloromycetin and aureomycin, p. 379 have been found more effective. *Streptococci*, *staphylococci*, *B. proteus* and *B. typhosus* infection: Acidify the urine and give hexamine, p. 706, caprokol or neotropin (see above). In strepto. and staphylo. infections saline diuretics with sulphonamide are more useful: also specific vaccine. Penicillin, p. 370, streptomycin, p. 377 and chloromycetin and aureomycin are useful in many infections. In *tubercular infection*, streptomycin is administered with P.A.S., p. 381. Minute doses of tuberculin, p. 728 is occasionally given.

Bed-sore.—If sores have formed, spray with acriflavine 0.1% with tannic acid $2\frac{1}{2}\%$. Frequently change side of a bed-ridden patient. The bed should be soft with no creases and if necessary, give air cushion. The back should be washed daily and alcohol 90% applied. Also, f. 46, 101, 228, 235, 284, 310, 333 and silver nitrate, p. 433. A clean sore epithelialize with scarlet red ointment, p. 177. If sloughing, f. 127 and urea, p. 699. *Prophylaxis*: Apply, f. 293, 310.

Beri-beri.—Stop rice and give vitamin B₁ containing food, p. 750; especially yeast and rice-polishing: also aneurine hydrochloride, p. 292. Absolute rest. Digitalis if congestive failure, p. 655 or ephedrine, p. 626 for vascular failure. Amyl nitrite, p. 667 for sudden heart attack also oxygen, p. 558: strychnine hypodermically, f. 397, 398 and nikethamide, p. 556 and leptazol, p. 557.

Bleeding, internal.—Treat the cause. Ca. salt orally also by injection, p. 272. Vitamin K products, p. 289. Also normal horse serum, p. 707 and thromboplastin, coagulen, p. 638; congo red, p. 177. Recently, viper venom, p. 639: toluidine blue, p. 177 and protamine sulphate, p. 641 are proving more useful.

Bleeding, superficial.—*Locally*, f. 49, 300: also adrenaline, p. 620 and viper venom, p. 639 and local pressure.

Boils.—*Locally*, if staphylococcal, gentian violet or brilliant green 1% ointment, p. 176: also f. 226. *Internally*, sulphonamides, p. 364 and 365 *orally*, also autovaccine, *hypodermically*. Penicillin, p. 375.

Bronchitis acute and Broncho-pneumonia.—Rest in bed and mostly liquid diet. *Locally*, f. 12, 13, 25, 28 by inhalation or spray if pharyngitis is associated: also f. 6, 7, 16 and kaolin poultice, p. 140 for application on the chest. *Internally*, sulphathiazol or sulphadiazine, p. 364, 365 also f. 2, 174, 176, 257 to 259, afterwards f. 260, 473 to 475, 483, 485: for irritating cough, f. 37, 243, 244, 349, 350, 351, 356, 455, 470. Penicillin esp. estophan and leocylin, p. 736 has advocates. As stimulant, f. 21, 365, 397, 398, 451: cardiazol and coramine, p. 556. Oxygen, p. 558. For delayed resolution, autogenous vaccine and f. 71.

Bronchitis, chronic.—Removal to a healthy dry atmosphere. If expectoration is foetid, by inhalation, f. 10, 12, 13, 34 ; internally, f. 22, 35, 36, 43, 100, 183, 257 to 260, 348, 354, 355, 450, 453, 454, 473 to 476 and autogenous vaccine.

Bronchiectasis.—If after chronic or recurrent attacks of bronchitis and delayed resolution of pneumonia, improve general health : also respiratory exercise and mixed vaccine : penicillin, p. 736 : inhalation, f. 10, 24, 69, 93, 94 : *orally* f. 35, 36, 43, 96, 482 : vitamins A and D with calcium. Drainage by postural change : lobectomy in suitable cases.

Black-water Fever.—*Prophylactic* : treat all malaria cases effectively in the first attack, see p. 349. Those having frequent relapses or susceptible to quinine should leave the endemic area. *Curative* : for vomiting, f. 221, 225, 306, 307 followed by f. 124, 128, 393 to 395 till the bowels move ; also f. 166, 167, 170, 175 till the urine is copious and alkaline. Cholesterol, p. 284. Specific treatment is atebirin orally and atebirin musonate intramuscularly, p. 348. If quinine is to be given, it is in $\frac{1}{4}$ gr. dose every hour and give 8 doses on first day. If no disturbance, rapidly increase. Paludrine, p. 348. For anæmia, f. 271 to 275.

Bruise.—To apply with a lint, f. 18, 282, 308, 309.

Burns.—Tannic acid, p. 144 also f. 46, 47. Triple dye, p. 176. Silver nitrate, p. 433 : afterwards if necessary cod-liver oil, p. 286. Treat the shock with radiant heat, blood plasma injection, p. 735 and stimulants.

Cancerum Oris.—Cauterise with f. 59, 300 also permanganate, p. 154 ; phenol, p. 166 ; nitric acid, p. 259 and trichloroacetic acid, p. 260. Apply, f. 127 or urea, p. 699 and afterwards acriflavine compress, p. 176 ; also autogenous vaccine hypodermically. Improve the general condition. If associated with K.A., specific treatment, p. 331. Sulphonamide, p. 366 and penicillin, p. 372 also useful.

Carbuncle.—Locally f. 127 and urea, p. 699 : sulphonamide, p. 366, penicillin, p. 372 and autogenous vaccine. Look for any associated debilitating factor, esp. diabetes mellitus.

Carcinoma.—X-rays and radium, p. 753. Nitrogen mustard, p. 121 and aminopterin, p. 297. Cobra toxin, p. 551.

Caries Dental.—For pain, phenol, p. 165 ; creosote, p. 178, also f. 325, 331. Internally, calcium, p. 269 ; calciferol, p. 283. Tonsil-adenoids if enlarged, should be removed.

Catarrh.—Naso-pharyngeal and cold, see **Coryza**.

Cellulitis.—Locally, sod. sulph., p. 209 and mag. sulph., p. 210 also f. 127 and urea, p. 699. Cataplasm. kaolini, p. 140. Orally, sulphonamide, p. 366. Penicillin, p. 372, Inj. of iodine, f. 71 also autogenous vaccine.

Cerebro-Spinal Fever.—Lumbar puncture : administration of serum has been replaced by sulphathiazole and sulphadiazine, p. 364, 365. Penicillin, p. 375. General treatment as care of the eyes (f. 102, also liquid paraffin), back, mouth, nourishment and elimination. Suprarenal cortex, p. 387, may be necessary in fulminating cases with hæmorrhage into the suprarenals.

Chancroid.—Compress the part with f. 202, 206 and if not very purulent apply, f. 73. *Orally*, sulphonamide, p. 361.

Chicken-pox.—*Orally*, f. 169, 170, 174 and sulphathiazole, p. 364 : *Locally*, sponge with 1 in 2000 warm permanganate lotion ; when scabbing, f. 296, 297. The patients should be isolated till all scabs separate.

Cholecystitis.—Purgative, f. 221, 225, followed by f. 123, 124, repeated as required in smaller doses : also f. 149, 156 to 158 and Taxol, Pancrobilin, Veracolate, Bicolate or Biledase, p. 694 to keep the bowels free. In addition, f. 491 and Cylotropine, p. 707 intravenously. Olive oil, p. 100. Dehydrocholic acid, p. 694. Felamine, Bilamide, Boldine, p. 695 ; stock or autogenous vaccine from bile aspirated by duodenal tube.

Cholera.—*Prophylactic*, vaccine, p. 729 : 4000 million, followed in one week by 8000 million : protection for 6 months ; also careful disposal of the excreta of the patient. *Curative*, sulphonamides, p. 365 ; bacteriophage, unsatisfactory : kaolin and charcoal, p. 141 ; for vomiting, f. 307 and 334 (in half doses and f. 410. If collapsed, blood pressure below 70 mm. Hg. and sp. gr. of blood above 1058 with obvious signs of dehydration, normal saline, f. 159, 160, 161 subcutaneously 1 pint : or intravenously, f. 159 to 161, 2 to 5 pints (according to the intensity of dehydration) and repeated when necessary. Hypertonic saline, f. 164 is indicated in the acute stage with profuse evacuations. If uræmia is threatening and in all late cases, f. 173, 1 pint intravenously (the rest may be normal saline) and f. 166, 167, 170 should also be given orally. Further fluid should be given freely orally and per rectum, f. 160, 161. Adrenaline chloride solution $\frac{1}{2}$ to 1 c.c. intravenously along with saline infusion. *Diet*, during the active stage, glucose and lactose, p. 107 and green cocoanut water ; afterwards liquids and semisolids.

Colic.—*Intestinal* : open out the bowels, f. 5, 8, 142, also f. 9 and purgatives, f. 128, 141, 149, 221, 225 : antispasmodics f. 29, 32, 316, 317, 318, 359, 432 : if severe pain, morphine as f. 343 also pethidine, p. 522 : syntrophane and trasentin, p. 616. *Renal*, f. 343 followed by f. 328 : afterwards f. 167, 168, 170, 174, 175 also thialion, p. 257 and urodonal, p. 707 along with plenty of water to drink. *Biliary* : f. 343. Afterwards f. 491 and dehydrocholic acid, p. 694 : boldine, felamine, p. 695 : olive oil, p. 100, mag. sulph., p. 212 ; other analgesics used during colic

are eukodal, eupaco, p. 521 ; amidone, p. 523 ; veramon, p. 487 ; novalgin, p. 529 ; pethidine, p. 522 ; syntrophon and trasentin, p. 616, benzyl benzoate, p. 679 : f. 472.

Coliform B. Infection.—See **Bacilluria**.

Conjunctivitis.—Wear coloured glass and forment the eyes. Apply f. 102, 205, 284, 289, 290, 292, 305, 357, 406 ; also mercurochrome, p. 313.

Constipation.—Administration of purgatives, p. 203. Regulate diet, which should have a fair amount of roughages and fluid. Constipation causing no symptoms should be left alone. Irritant purgatives are not to be frequently repeated.

Constipation of children.—Adjust diet : also f. 132, 141, 147, 148 : milk of magnesia, p. 214 and castor oil, p. 219.

Constipation habitual.—Liquid paraffin and its preparations, p. 103 also plantago ovata, p. 94. These may be helped by f. 136, 143, 150, 151, 256, 393, 394, 395, 433, 434.

Constipation with hypertension.—A hydragogue morning evacuation is often helpful, f. 129, 130, 131, 149 also Kruschen salt, p. 214 and f. 393 to 395.

Constipation with sluggish liver.—Restrict fatty, spicy food, ensure physical exercise also f. 123, 124, 128, 146, 156 to 158.

Convulsion.—Treat the cause. Put the patient in bed ; loosen clothes, restrain movements and put paddings between the teeth : f. 328, 329 : anticonvulsants, p. 495, 501 : soluble phenobarbital, p. 496 : paraldehyde, p. 500 : hyoscine hydrobromide, p. 614 hypodermically even chloroform inhalation : or if severe, evipan sodium, p. 497 or sod. thiopentone, p. 498 and sodium amytal and somnifaine, p. 498 intravenously.

Corn.—Apply, f. 380 repeatedly. The superficial layers are gradually worn out.

Cornea, ulceration.—Pad and bandage : dilate the pupil by f. 429 and 430 : apply sulphacetamide, p. 365 or penicillin, p. 371.

Coronary Thrombosis.—Rest in bed for about 3 months from the date of attack. For mild pain, veramon, p. 499 : eukodal, p. 521 : amidone, p. 523 or better hypodermically morphine, p. 510 : f. 343 : This may be followed by oral analgesics. No nitrites. Heparin, p. 640 and dicoumarol, p. 642. Digitalis if congestive failure : afterwards aminophylline, p. 533. Investigate the cardiovascular condition as a whole and fix up the mode of life.

Coryza, Rhinitis.—*Locally*, f. 13, 25, 64, 81, 106, 332 also ephedrine, p. 624 and benzedrine, p. 627. *Internally*, f. 170, 251, 372, 373, 388, 389, 462. Dover's powder, p. 512. Sulphonamides, p. 366. Antihistamines, p. 673.

Cough, irritable.—Investigate the cause : f. 36, 37, 96, 100, 323, 348, 349, 351, 352, 455, 469, 470, 484, 485 : also see expect-

torants, p. 681. *With fætor*, Inhalation, f. 10, 34, 69, 93, 94, 110 : Sulphonamides, p. 366. Antibiotics, p. 370, 736. Supportive treatment by stimulants and nourishments.

Cretinism.—See p. 407.

Cystitis.—Urinary antiseptics, p. 705 : f. 108, 479, 480 ; also see Bacilluria. Locally, bladder wash : pot. permang. 1 in 2000, silver nitrate 1 in 1000, mercurochrome $\frac{1}{2}$ to 1% or proflavine 1 in 2000. Obstruction if any, should be removed.

Debility.—Treat the cause. General tonics, f. 195-196, 200, 201, 238, 239, 274, 279, 396. Also vitamin B., p. 298 and multivit., p. 301.

Dermatitis.—Inflammation of the skin may be associated with exudation : for *bath*, f. 165 and Cetavlon, p. 102 : to *apply*, f. 47, 76, 190, 283, 299. Antihistamines, p. 672. Thyroideum, p. 407. Vitamin A, p. 280.

Diabetes Mellitus.—In milder cases of over-eating obese male, starvation till the urine is sugar-free followed by food starting with vegetables containing 5 to 10% of carbohydrates. Watch both the blood and urine sugar. With rest and restricted diet, he may be able to increase his carbohydrate tolerance. Average working man requires about 350 gm. of carbohydrate, 100 gm. of protein and 80 gm. of fat (about 2500 calories). If even 150 gm. of carbohydrate causes glycosuria, give insulin, p. 412. If there is acetone in the urine, give glucose and insulin in big dose, p. 414. Insulin substitutes, p. 416 are of no substantial value. Attend to other associated pathological processes especially associated septic conditions. For neuritis, vitamin B₁, p. 292.

Diabetes Insipidus.—Post. pituitary ext. p. 404.

Diarrhœa.—If due to *unsuitable food*, f. 125, 128, 141, 221, 225. Afterwards f. 19, 50, 51, 53, 87, 90, 121, 182, 191, 192, 229-231, 236, 313, 345, 360, 391 : also kaolin, p. 140, wood charcoal, p. 141 and sulphonamides, p. 365.

If *chronic*, find out the etiology and treat. *Diet* should be restricted to liquids only during the active stage and gradually increased.

Diphtheria.—(i) *Prophylaxis*, p. 723. (ii) *Curative* : Rest in bed. Specific serum, p. 724. *Locally*, f. 12, 13, 25, 28, 34, 54, 56, 64. *Externally*, kaolin poultice, p. 140. *Orally*, f. 22, 169, 170, 174, 176. For heart failure, f. 21, 314, 316, 365, 397, 398, 426, 427, 451 also adrenaline, p. 622, coramine, cardiazol, oxygen, p. 555 to 558. For increasing toxæmia, glucose and insulin in addition, p. 415. For septic throat infection and for pneumonia, sulphadiazine, p. 365 and penicillin, p. 375. For muscular paralysis, vitamin B₁ hypodermically, p. 292.

Duodenal Ulcer.—See Gastric ulcer.

Dysentery, amœbic.—Rest in bed. Castor oil 1 oz. Then f. 233, 263, 264 : f. 131 one or 2 doses every morning and emetine, p. 352 hypodermically and oral amœbicides, p. 353 and 356. Aureomycin, p. 379, may be used. *Scheme of treatment*, p. 356.

Dysentery, bacillary.—Rest in bed. Purgative a dose of castor oil (this clears the upper bowels): sulphaguanidine, p. 365 and succinylsulphathiazole, p. 366 are given : later on ispaghula, p. 94 also paraffin emulsions prevent after-constipation : for tenesmus, f. 342. Shiga serum are now seldom used. In chronic cases, bowel wash with normal saline, hypertonic saline with sugar, permanganate (1 in 2000), acriflavine (1 in 2000), tannic acid (1%) or silver nitrate (1 in 1000). Diet, lactose and peptonised milk only during the active stage.

Dysmenorrhœa.—Treat the local condition. Hot water hip bath. Sedative f. 319, 344, 362, 472 ; eupaco, eukodal, p. 521 ; veramon, ailonal, p. 499 ; pethidine, p. 522 and amidone, p. 523 ; veganin, g. 541 ; saridon, p. 542 ; bellergal, syntrophon, trasentin, p. 616. Follicular products, p. 396.

Dyspepsia.—Treat the cause. Remove focal sepsis. Diet should be light, nourishing and yet palatable. For improving appetite and digestion, give f. 118 to 121, 145, 150, 180, 181, 245, 246, 312, 346, 347, 399 to 401. Digestants, p. 200 ; vitamin B complex, p. 292, 293.

Carbohydrate dyspepsia.—All root vegetables, green peas, lentils, banana and rice are restricted. Digestives as pancreatin, p. 200, papain and diastase, p. 201.

Eczema.—Remove the cause. If *acute*, lotio calaminæ, p. 50 and lotions as f. 47, 76, 137, 189, 190, 283, 297. If much *crusting*, starch poultice. If *extensive*, bath f. 165. If *chronic*, ointments as f. 15, 46, 139, 209, 296, 298. Unna's paste, p. 435 and Lassar's paste, p. 437. Correct focal sepsis, constipation, anæmia and other constitution disorders. *Orally*, Thyroid gland, p. 407 in increasing doses ; antiallergic preparations, p. 673 : also mixed strepto.-vaccine hypodermically.

Endometritis.—Remove the cause : improve general health ; hot vaginal lavage with f. 81, 109, 287, 291 : permang., p. 154 : iodine, p. 158 : chloroxylenol, dettol, p. 170 : non-specific protein therapy, p. 733.

Enuresis.—Investigate and treat the local conditions in the genitals and throat : also helminthiasis if present. Improve general hygiene. Tinct. Bellad. min. 10 at bed time for a child of 6, may be combined with camph. monobrom. gr. 3 and the dose may be increased ; ephedrine, p. 625 and amphetamine, p. 628 are also given.

Enteric Fever.—*Prophylactic*, T.A.B. vaccine, p. 729, bili-vaccine, p. 729 : *Curative* : Absolute bed rest : no purgative after first week : open the bowels by enema every other day and liq. paraffin orally when convalescence is nearing. If no

complications except slight bronchial catarrh, f. 169, 170 in half doses. *Oral hygiene* : f. 27, 30, 54, 57, 103, 104 : also hydrogen peroxide, p. 150 : boroglycerin, p. 180 ; mercurochrome, p. 313. To the back, alcohol 90% and f. 101. The *specific treatment* is with chloromycetin which succeeds in a large percentage of cases, p. 379. The initial loading dose may be given 2 every 2 hours and in non-toxic cases half hourly. The liberated typhoid endotoxin may cause vaso-motor depression and each dose of chloromycetin may be preceded by 15 minims of nikitamide. For *high temperature*, ice cap and tepid sponging, p. 238. For *diarrhœa*, limit food ; kaolin, p. 140 and creta, p. 274. For *flatulence*, all food by mouth stopped and 5% glucose is given subcutaneously or slowly intravenously, 1 to 2 pints once or twice daily : charcoal, p. 141 : liq. ferr. perchlor. min. 15 t.d. also flatus tube. For *hæmorrhage* : stop all food ; morphine, gr. $\frac{1}{6}$ hypodermically : vitamin K, p. 288 ; calc. glucon., p. 272 ; congo red and toluidine blue, p. 177 ; protamine sulphate, p. 641 ; normal horse serum, antistrept. serum (10 to 20 c.c.), hæmoplastin 2 c.c. For heart failure, caffeine sodium benzoate, p. 526 and f. 365 ; cardiazol, coramine, p. 556 ; strychnine, f. 397, 398. For *lung complications*, see bronchopneumonia. *Diet* : whey, lactose, glucose, p. 108 ; dextrimaltose, p. 110 ; peptonised milk, p. 200 : protein hydrolysate, p. 736. During convalescence, rice gruel, typhoid bread, sooji gruel and soft rice successively.

Epidemic Dropsy.—Rest in bed. Stop rice and mustard oil. Keep the bowels regular by paraffin emulsion, p. 103 or f. 141 ; Calcium by mouth also intramuscularly or intravenously, p. 272. If much right heart stasis, digitalis. If dyspnœa without much cardiac stasis, ephedrine, p. 625. Also probably vitamin B₁, p. 292. Restrict meat and eggs (these form toxic amines) also much cellulose-containing vegetables (these increase flatulence). Peptonised milk food is preferable.

Epilepsy.—Stop all reflex irritations. Sedatives as bromide and phenobarbitone, f. 320, 321, 336, 338 : methylphenobarbitone, p. 497, phenytoin, p. 502 and mesantoin, p. 504. For *minor fits*, tridione, p. 504. For status epilepticus, paraldehyde per rectum, p. 500 or sodium phenobarbitone or amytal sodium, p. 496, 498, parenterally may do.

Erysipelas.—*Locally*, f. 65, 78 also brilliant green, p. 176. *Orally*, sulphonamide, p. 363 ; penicillin, p. 370 also specific serum and vaccine.

Fever Catarrhal.—f. 174, 176, 251, 258, 259, 350, 388, 389 also a preliminary purgative, p. 204.

Fibrositis.—See Lumbago.

Filariasis.—During acute exacerbation, the affected limb is elevated and f. 282, 308 applied : also f. 372, 375, 377 orally. *Specific drug* is Benocide or Hetrazan, p. 335. Tryparsamide,

p. 323 ; soamin, p. 323 ; antimony, p. 332 and T.A.B. vaccine, p. 729 are also sometimes used.

Flatulence.—Keep the bowels regular by f. 143, 148, 151, 156 to 158 and bile salt purgatives, p. 694 ; give suitable diet containing less carbohydrate and cellulose and also f. 118 to 121. Intestinal antiseptics, p. 691 ; carminatives f. 20, 29, 45, 316, 317, 318 ; digestants, p. 199. If much flatulence, high tube enema, f. 5, 8 ; Turpentine stupe, p. 118 : prostigmin, p. 596 : acetyl choline, mecholyl, doryl, p. 591.

Gas-gangrene.—Prophylactic, curative, serum, p. 725 ; Sulphonamides, p. 363 ; penicillin, p. 370. Supportive treatment and surgical measures.

Gastric Ulcer.—With rest in bed for 3 to 6 weeks, 4 to 6 oz. of milk with 10 gr. of sodium citrate is given every other hour from 8 A.M. to 10 P.M. ; alternating with it, every other hour, arrowroot, junket, Benger's food, custard or fruit jelly ; a week after in addition, twice daily mashed potato or cauliflower. For the night, some citrated milk is kept ready and sipped if acidity is felt. Olive oil immediately before 3 of the feeds and atropine sulphate 1/50 gr. before 3 other feeds and in double dose at bed time : this may be increased till dryness in the mouth is complained of : see Antacids, p. 688. A powder containing 10 grs. of magnesium oxide with 30 grs. of kaolin, 30 grs. of magnesium trisilicate, p. 213 or 30 grs. of aluminium hydroxide, p. 141 is taken in the morning and at the middle of the day and in double dose at bed-time also whenever the patient feels any acidity. In most cases, hourly feeds need not be given : liquid meals at 1 and 6 A.M. (if awake) and at 10 A.M., 2 P.M., 4 P.M. 8 P.M. and 10 P.M. and semisolids (as boiled fish, chicken or soft vegetables, toasts, biscuits and soft boiled rice) at 8 A.M., 12 noon and 6 P.M. Food is progressively increased which should be bland and non-irritating for several months. Sippy method, f. 171 is now obsolete. Mucin, p. 688 ; larostidin p. 662 are sometimes used. Mouth and teeth are to be kept clean and smoking stopped. To ensure complete mental relaxation, phenobarbitone ½ grain should be given 3 times daily. Ascorbic acid 50 mg. 2 or 3 times daily is helpful.

Gastritis Chronic.—Wash the stomach with or give as drink sod. bicarb. 60 grs. in one pint of warm water in the morning ; open out the bowels, f. 141, 220, 221. For vomiting, f. 26, 95, 225, 229, 306, 307, 468 : stop all irritating factors. Diet is bland as citrated milk to start with. Hydrochloric acid diluted, 20 to 30 minim in 4 ounce of water is sipped after the principal meals.

Gingivitis.—Keep the mouth very clean (see stomatitis) and apply, f. 30, 460 : internally, vitamin C, p. 299.

Glands, Lymphatic.—Inflammation of, apply, f. 67, 68, 79, 97, 211, 425 also specific treatment.

Glaucoma.—f. 416, 417, sometimes neostigmine, p. 597 and pilocarpine, p. 598. Also purgative f. 123, 124, 131. Surgical treatment.

Goitre, Endemic.—This is endemic in some places. Ensure pure water supply and working of the bowels. Liq. iod. aquosus, p. 160. Iodised salt, p. 265. Intestinal antiseptics, p. 691.

Ex-ophthalmic.—Iodine, p. 160, 265. Thiouracil, methylthiouracil, p. 409. Subtotal thyroidectomy: X-rays and radium, p. 753: Rest and sedatives.

Gonorrhœa, Prophylactic.—f. 288. If acute, orally, f. 168, 174, 175. Penicillin, p. 375 is highly successful and gives quickest cure: also sulphathiazole and sulphacetamide, p. 366, 381.

Gout.—Meat should be restricted especially the glands and brain, also tea, coffee and alcohol. Saline purgatives, f. 123, 124, 128, 131. During an attack, colchicum: f. 420 to 423. Afterwards cinchophen, p. 549. Also f. 177. *Locally*, f. 23, 67, 68, 79, 425.

G.P.I.—Antisymphilitic treatment with penicillin, p. 375: pot. iod. with mercury orally, f. 217 should be the first choice. Tryparsamide, p. 323. Malarial infection by injecting blood containing the B.T. parasites is helpful: pyretotherapy, p. 535.

Granuloma Venereum.—Antimony, p. 332. Chloromycetin, p. 379.

Hæmoptysis.—Treat the cause. If *tubercular*, rest in bed: morphine, gr. $\frac{1}{6}$ hypodermically: inhalation, f. 110; amyl nitrite, p. 669: cough sedative, p. 763. See bleeding, internal, p. 760.

Hæmatemesis.—Absolute rest: no food or drink by mouth: ice to suck and a small ice-bag on the epigastrium. In peptic ulcer, frequent sips of iced citrated milk is helpful which neutralizes the corrosive acid. Adrenaline chlor. sol. 60 min. after careful stomach wash; morphine $\frac{1}{4}$ gr. hypodermically: See *Bleeding*, internal, p. 760. Rectal and subcutaneous glucose 5% even blood transfusion.

Hair Dye.—f. 286.

Headache.—Remove the cause. *Locally*, f. 24, 385. *Internally*, f. 373, 376 to 379. Also p. 542.

Heart, decompensation.—See, *Anasarca*, cardiac; *Peripheral* (vaso-motor) *failure* adrenaline, p. 622: ephedrine, p. 625; strychnine, f. 397, 398; leptazol, p. 557: nikethamide, p. 556, post. pituitary, p. 402; caffeine, p. 531. *Heart Block* (partial) hypodermically atropine, p. 609 and adrenaline, p. 620; orally ephedrine, p. 625 and barium chloride, p. 231. Subsequently when the ventricles have resumed their own rhythm and the block is complete, digitalis. *Acute myocardial failure*, digitalis, p. 655. *Endocarditis, bacterial*, penicillin, p. 375: streptomycin, p. 377 and combiotic, p. 378. See *Auricular fibrillation*, p. 759; *Coronary thrombosis*, p. 763: *Syncope*, p. 175.

Hepatitis.—If due to acute indigestion or infective, f. 123, 124, 128, 221. If with cholangitis, f. 491. If following dysentery, treat for amœbiasis, p. 356. *Diet*, p. 695.

Herpes Zoster.—*Locally*, f. 46, 47, 326, 333, also ultraviolet rays, diathermy, p. 755. *Internally*, for pain and sedation, f. 338, 372, 373, 376, 379. Allonal, didial and veramon, p. 499; Dilaudid, eukadol, p. 521; Pethidine, amidone, p. 523. Also post. pituitary ext. $\frac{1}{2}$ to 1 c.c. intramuscularly daily, p. 404. Specific action is claimed of chloromycetin, p. 379.

Hiccough.—Remove the cause. *Sedatives* as phenobarbitone, p. 496: chloretone, p. 490: *antispasmodics* as papaverine, p. 516: omnopon, p. 521: belladonna, p. 609: adrenaline, p. 621 and nitrites, p. 667. Also f. 26. Mustard plaster on the epigastrium. Blister or ethyl chloride spray over phrenic nerve. Atropine sulphate, gr. 1/60 hypodermically, p. 609. Belladenal, p. 616.

Hodgkin's Disease.—X-ray therapy, p. 753. Nitrogen mustard, p. 121.

Hypertension.—Correct focal sepsis. Ensure one relaxed motion daily, see p. 211: by f. 123, 124, 128, 130, 131 or by Kruschen salts, p. 214: pulv. glycyrrh. co., p. 216. Lessen worry and excitement: if insomnia, f. 319, 335: also p. 498. Low protein diet: rice diet with less salt, p. 244. Protoveratrine, p. 663. Nitrites, p. 669: Lacarnol: padutin, mistletoe, p. 670: rauwolfia serpentina, p. 525: sympatholytic agents, p. 628: sulphocyanate, thiocyanate, p. 677: pot. iod. p. 266. Acetyl choline, doryl, mecholyl, p. 590.

Hypothyroidism.—*Cretinism*: *Myxœdema*, See p. 407.

Hysteria.—Suggestion, isolation, attention to general health, especially to pelvic disturbances and give f. 32, 33, 299, 322; elixir bromovalerinate, p. 486. During fits, f. 41.

Impotence.—Remove the cause. Gonadotropic preparation, p. 400: also vitamin E, p. 287.

Influenza.—*Prophylaxis*: segregation of the patient and avoid overcrowding. *Curative*: rest in bed and for *pharyngeal catarrh*, f. 58, 64, 66, 92, 463: also p. 512: for *pains and aches*, f. 367, 372, 373, 376, 389; for *bronchial catarrh*, f. 90, 169, 176 and 251: streptomycin, p. 381: sulphadiazine, sulphathiazole and penicillin for the secondary infection. For *heart failure*, nikethamide, leptazol, p. 556: adrenaline, p. 622: ephedrine, p. 625: strychnine, p. 565: caffeine, p. 528: also f. 365, 397, 398 and 451. Symptomatic measures.

Insomnia.—Find out the cause. If without pain, f. 319, 320, 327, 339: also see p. 500. If with pain, morphine, p. 508.

Intestinal Obstruction, Partial.—f. 5, 8, 141, 142. If complete, surgical treatment.

Iritis.—Atropine, f. 428. Also treat the cause.

Jaundice acute catarrhal or infective.—Rest : fomentation on the liver, cataplasma kaolin, p. 140 ; also f. 220, 221, 225 : followed by f. 123, 128, 131 : also f. 491 and intravenous hexamine 40% or cytotropine 5 c.c., p. 707 with glucose 12½% 25 c.c. every other day. Diet, liquid if febrile : carbohydrate and protein need not be restricted but should be nearly fat-free. Essential amino-acids, p. 695.

Kala-azar.—Antimony, p. 331. Avoid diarrhoea, dysentery, pulmonary catarrh, hepatic and renal complications also sepsis. Further, iron, f. 273 to 277.

Lamblia Intestinalis, *giardia intestinalis* : mepracrine, p. 347 often cures : 2 or 3 courses at 2 weeks' interval may need. For colonic catarrh, plantago ovata, p. 94 and f. 44.

Laryngitis.—Treat the cause ; Cataplasma kaolin., p. 140 externally. Inhalation, f. 10, 12, 34, 69, 93, 94, 110. Spray, f. 13, 25, 28, 64, 332, 403. For irritable cough, f. 37, 323, 349, 351, 356, 358.

Laxatives.—For mild action of the bowels, f. 53 : paraffin emulsions, p. 103 : sulphur, p. 216 : agar, p. 218 : ispaghula, p. 94 : castor oil, p. 219.

Leprosy.—Specific, Hydnocarpus oil, p. 383 : sulphones, p. 383 : trichloroacetic acid locally, p. 260 : segregation. For nerve pain, adrenaline and ephedrine. Improve general health.

Leucoderma.—Locally, f. 17. Correct intestinal disorder if any present and improve the general health.

Leucorrhœa.—For douching, f. 60, 109, 217, 381. Also iodine, p. 158 : dettol, p. 170 : lysol, p. 170 : S.T.37, p. 172 : choleval, collargol, p. 434 : also stovarsol vaginal compound tablet, p. 324 applied to fornix after sod. bicarb. douche once or twice daily ; improve the general health and also treat the local condition if any.

Leukæmia.—Liq. arsenicalis, p. 319 in increasing doses : urethane, p. 499 : also radiophosphorus, p. 277 and aminopterin, p. 297. X-rays provided anæmia is not marked and not running high temperature also radium, on the long bones and spleen : these are more favoured.

Liver.—Hepatitis, p. 769 : Jaundice, p. 770 : Abscess, p. 757 : Cirrhosis, (a) in the early stage, bowels are opened, f. 123, 128, 156 to 159 and bile salts, p. 694 : diet, bland, p. 695 : glucose, p. 107 : no alcohol. (b) If with ascites, ammon. chlor., p. 703 and mercurial diuretics, p. 310.

Locomotor Ataxy.—Antisymphilitic : penicillin, p. 375. Better to start with mercury, p. 308 ; arsenobenzol, p. 327 ; tryparsamide, p. 323 and bismuth, p. 316 ; Hg. and Kl, f. 217, for two months between the courses are given. Pyretotherapy, p. 535 is of some value. Symptomatic treatment : massage and re-education by graduated movements of the affected limbs.

Lumbago.—*Locally*, f. 6, 7, 16, 23, 39, 67, 384, 385. Open out bowels, f. 123, 124, 128, 131, 220 : Kruschen salt, p. 214 : next *orally*, f. 367, 373, 386, 387 : Pot. iod., p. 265 : cinchophen, p. 549 : *parenterally*, iodine, f. 72 and entodon and iodeol, p. 161 : sulphur, p. 216 : irgapyrin, p. 548 and milk protein, p. 733 : Diathermy, infra-red rays, p. 755. Correct focal sepsis.

Lymphangitis.—Treat the cause. For chronic glandular enlargement, f. 211, 213.

Lymphogranuloma Inguinale.—*Orally*, sulphonamides, p. 361, chloromycetin and aureomycin, p. 379.

Malaria.—Open out the bowels by f. 220, 221, 225 followed by f. 123, 125, 128, 130, 131 and one dose every morning, if required. Alkalies, f. 167, 170 and 174, $\frac{1}{2}$ to 1 hour before each dose of quinine or mepacrine and f. 247 to 250 and 252 to 255. During convalescence, f. 241, 242, 272, 274 : also esanofele and quinostovarsol, p. 350. See *Scheme for the Treatment of Malaria*, p. 349.

Mastitis.—Apply, f. 425, 431 and bandage, lifting and supporting the breasts. Gonadotropic hormones, p. 396.

Measles.—*Specific*, p. 732. *Internally*, f. 169, 176, 257, 259.

Meniere's Disease.—Sedatives as bromide, p. 484 : phenobarbitone (gr. $\frac{1}{4}$, 4 times daily), p. 496 : aspirin, p. 547 : benadryl, p. 673 : Nicotinic acid, p. 295. Potassium chloride, p. 252.

Menorrhagia.—Treat the cause ; also f. 361, 495 to 498, 500. Calc. glucon. by mouth, intramuscularly or intravenously. Gonadotropic preparations, p. 397. Local treatment.

Migraine.—*Locally*, f. 24, 385. *Internally*, sedatives, f. 330, 367, 376 to 379, 413 : also luminal, f. 335 ; veramon, p. 499, sonalgin, p. 498 : vaso-dilators, p. 669 : pot. chlor., p. 252. Ergotamine tartrate, p. 712. Investigate for any error of refraction, hepatic or menstrual disorder.

Muscular Pain.—See *Lumbago*.

Mumps, locally.—f. 4, 79, 97. *Gargle*, f. 27, 31, 54, 81, 86, 104, 105, 162. *Orally*, f. 168 : chloromycetin, p. 379.

Myasthenia Gravis.—Physostigmine, p. 592, neostigmine, p. 597 (if these cause abdominal discomfort, atropine may be combined) : also ephedrine, p. 624 : glycine, p. 262. Deep X-rays on the thymus occasionally helps.

Myocarditis, Acute simple.—Absolute rest for 6 weeks or more till the pulse rate is normal with moderate exercise : f. 386, 387, if rheumatic fever is associated. For heart failure, f. 397, 398 ; nikethamide, p. 555 ; leptazol, p. 557 ; adrenaline, p. 622 ; ephedrine, p. 625 ; digitalis, p. 655.

Nephritis.—*If acute*, keep the patient warm in bed. Open out the bowels, f. 128, 129. Next, f. 167, 170, 174, 175 : if septic tonsillitis is present, penicillin, p. 371. Antihistamine,

p. 673. *Diet* : Liquid, carbohydrate esp. glucose and fruit juice ; fluid up to 2 pints. As the condition improves, toast, biscuit and skimmed milk. *If subacute* with general anasarca, purgation with jalap, p. 227 ; also f. 128, 129 and p. 204. Diuretics as f. 126, 185, 456, 457, 465, 466, 488, 490 ; urea, p. 699. *Diet* : skimmed milk, toast, afterwards boiled vegetables and fish ; if urea elimination is at least 2%, Epstein's diet (protein 100 to 200 gm., carbohydrate 200 to 300 gm, and fat 20 to 40 gm.). Fluid and salt are restricted.

If chronic, restrict diet (less protein), alcohol, tea and tobacco : regulate exertion and ensure good period of rest. Keep the bowels regular by f. 123, 124, 128, 129, 131. If blood pressure is high, see Hypertension, p. 769.

Nephrosis chronic.—*Rest* in warm bed : diuretics as urea, p. 699 : mercurials, p. 313, cautiously intramuscularly. Also Thyroid gland, p. 407. *Diet* : consists of more protein, less fat and salt free (this may be milk 30 oz., 2 eggs, fish 2 oz., salt free bread 5 oz., salt free butter 2 oz., sponge cake 1 oz., porridge 6 oz. and fruit 3½ oz. : *Schemm's diet*). Salt substitute, pot. chlor., p. 252.

Neuralgia.—Put the affected part in a comfortable position. *Locally*, f. 23, 315, 317, 326, 423, 459. *Internally*, f. 339, 367, 376 to 379. Also pot. iod., p. 265. Alcohol (80%) or novocaine (0.5%) injection into the nerve trunk ; infra-red rays, diathermy and short wave therapy, p. 755.

Neurasthenia.—The cause is determined and treated. If indefinite, vitamin B complex, p. 298 : multivit., p. 301 : drinalfa, p. 626 and dexedrine, p. 628 also f. 396.

Night-blindness.—Vitamin A, p. 281 : if associated with obstructive jaundice, bile salts, p. 694, 695 also : if with multiple vitamin deficiency, p. 301.

Oriental Sore.—Antimony, p. 332 : berberine sulphate, p. 198. X-rays application, p. 753. Dithranol, p. 184 and Mepacrine (as 10% ointment), p. 347 are sometimes used : For mixed infection, sulphonamides or penicillin.

Otorrhœa.—Remove pus by swabbing frequently and drop, f. 84, 107 ; also proflavine, 1 in 1000, p. 175. Remove tonsils and adenoids. Autovaccine.

Oxaluria.—Stop vegetables like spinach, figs, beetroot, tomatoes and also tea. In *hypochlorhydric* cases with fermentation, give dilute hydrochloric acid along with food : f. 180. Also mag. sulph. (changes cal. oxalate to magnesium oxalate) and acid. sod. phosph., p. 702 which are solvents favouring easy excretion.

Pain, superficial.—To apply, f. 4, 6, 7, 16, 24, 39, 213, 315, 384, 385 : also see p. 543. *Internal*, Analgesics, p. 550 : morphine, f. 343 and p. 521 : pethidine, p. 522 : amidone, p. 523.

Palpitation.—Remove the cause. If due to neurosis, f. 33, 338, 461 ; cactina, p. 661. Also calcium preparations with parathyroid.

Paralysis Agitans.—Stramonium, p. 613 ; hyoscine, p. 615. Parpanit, p. 567 : antihistamines, p. 673 : myanesin, p. 567. For sleeplessness, f. 335. For pain, f. 373, 376 and p. 499.

Pediculosis.—p. 184, 185, also f. 207.

Piles.—Keep the stools soft. Paraffin emulsion, p. 103 ; compound liquorice powder, p. 215 ; also f. 128, 131, 136, 393. Locally, f. 48, 269, 341, 402, 409, 411 also Anusol, p. 317 ; Injection of ethanalamine, p. 637 : Injection of phenol, f. 85 also of sodium morrhuate, p. 286 : quinine and urethane, p. 363.

Pericarditis.—Absolute rest ; f. 386, 387 ; afterwards, f. 185 ; iodide may be gradually increased. Purgative, f. 128, 131 ; Counter-irritation on the precordium, p. 136 or f. 6, 7, 16, 39 ; iodex, p. 161. If effusion causing symptoms, paracentesis.

Pharyngitis.—If *acute, locally*, f. 1, 12, 13, 25, 28, 34, 56, 64, 69, 93, 94, 332, 448, 481, for sucking (lozenge), by inhalation and spray. See laryngitis ; for *painting*, f. 66, 91, 268, 285 ; also glyc. of tannic acid, p. 144 ; *gargle*, f. 27, 31, 54, 81, 269. *Orally*, f. 37, 169, 170, 243, 257, 258 ; if streptococcal, sulphonamide, p. 366 ; if rheumatic, salicylates, p. 545. If *chronic*, locally, f. 13, 28, 47, 66, 92, 285 ; also removal to a healthy dry atmosphere.

Plague.—Specific vaccine, p. 726 ; sulphadiazine, p. 365 and streptomycin, p. 378.

Pleurisy.—*Locally*, f. 6, 7, 16, 39, 67, 68, 211, 213, 384, 385 ; also iodex, iodolep, p. 161 ; strapping the side or artificial pneumothorax : infra-red rays, diathermy, p. 755 and short-wave therapy, p. 756. *Orally*, purgative, f. 124, 128 ; also as diaphoretic-diuretic, f. 170, 174, 176 ; for pain, f. 376 to 379, 387, 388. Iodides, p. 265. If effusion ; a small effusion is treated as above ; also p. 533. If big, not showing signs of absorption in three weeks and causing cardiac or respiratory distress, aspirate and fill the vacant space with air ; afterwards, change of climate.

Pneumonia, lobar.—Specific : sulphathiazol, sulphadiazine, p. 364-365 : penicillin, p. 375. For cyanosis, oxygen, p. 558. For elimination, by bowels, f. 220, 221, followed by f. 128, 393 in the first day afterwards by enema ; also f. 169, 170, 176, 257, 258, 323. When resolution is nearing, f. 257, 453, 454. For heart, caffeine, f. 365 : strychnine, f. 397, 398 : ephedrine, f. 451 : alcohol, p. 450 : leptazol, coramine, p. 556, 557. For insomnia, f. 327, 335 and p. 498.

Pneumonia primary atypical, virus.—The specifics are chloromycetin and aureomycin, p. 375.

Poisoning.—Stomach washing : Emetic : mustard and other emetics, p. 689.

Poisoning, by *alkaloids*.—Tannic acid, p. 145 and permanganates, in solution p. 154 : In addition, for *narcotics*, nikethamide, p. 555 : leptazol, p. 556 : caffeine, p. 528 : strychnine, p. 565 and for opium poisoning, atropine, p. 606. Picrotoxin, p. 554 : for *convulsants*, ch'loroform. chloralbrodide, f. 329 : paraldehyde, p. 500 and barbiturates, p. 427.

As., *Bi.* or *Hg.*, poisoning : sod. thiosulphate, p. 321 and B.A.L., p. 312 : also f. 281.

Heavy metals.—Stomach tube, emetic, p. 689 : egg white, mag. sulph. Also see under the respective metals. *Lead*, p. 212, 273, 703 : also p. 436.

Acids.—Creta and other alkalies : egg white and barley gruel : also see p. 262.

Iodine.—Stomach tube : emetic : thick barley water, saccharated lime water : also see p. 160.

Phenol.—Saccharated lime water, sod. sulph., mag. sulph., egg white : also see p. 169.

Phosphorus.—Copper sulphate 3 grs. well diluted every 5 minutes : pot. permang. 0.1% solution, oil of turpentine (not recommended). **Cyanides.**—See p. 183.

Polyneuritis.—Find out and remove the cause. Generally, vitamin B₁, 50 to 100 mg. daily intramuscularly *Locally*, f. 4, 23, 315, 326 : followed by f. 6, 7, 16, 39, 384. For *pain*, see Neuralgia, p. 772.

Post-partum Condition.—f. 493, 494 ; also see p. 714. As restorative, f. 271, 273 to 275 and vitamin A, B, C, D, E. Multivit., p. 301.

Prickly Heat.—The body is sponged with a watery solution containing 1 to 2% of salicylic acid, 0.1% mercury perchloride and 1 in 3 of rectified spirit : afterwards f. 293, 298.

Pruritus.—Bath f. 165. Antihistamines, p. 673. If localised, f. 283, 296, 297, 298, 412 : also amethocaine and cinchocaine ointment, p. 574. Investigate and remove the cause.

Pseudo-hypertrophic Muscular Dystrophy.—Glycine, p. 262. Vitamin E, p. 287 : 10 mg. or more along with vitamin A, 4 times daily has been recommended.

Psoriasis.—Locally pyrogallie acid, p. 146 also f. 14, 112, 134, 295 and orally liq. arsen. 2 min. gradually increased : colloid gold, p. 441 or manganese also thyroid extract, p. 407.

Purpura.—If bleeding, *locally*, thrombin, viper venom, p. 639 ; sodium or calcium alginate packing, p. 638 and *internally*, vitamin K, p. 289. Splenectomy.

Pyelitis.—Sulphonamide, p. 366 : sodium or ammonium mandelate, p. 704 ; also hexamine, p. 706 ; neotropin, pyridium, p. 177 ; caprokol, p. 172 ; penicillin, p. 370 ; streptomycin,

p. 378 ; chloromycetin and aureomycin, p. 379 ; autogenous vaccine ; also see Cystitis, p. 764.

Pyorrhœa Alveolaris.—Remove the lime concretions and open out pus pockets. Apply f. 27, 30, 31, 57, 81, 82, 86, 104, 105, 390, 460, 477 ; also hydrogen peroxide, p. 159 ; chloroxylenol, p. 170 ; mercurochrome, p. 313, "sanitas" fluid, glycothymoline, p. 127. Vitamin A, p. 281 : vitamin C, p. 300.

Raynaud's Disease.—The body especially the limbs should be kept warm : papaverine, p. 516 : carbachol, p. 591 : tetraethylammonium bromide, p. 629.

Rheumatic Fever.—Absolute rest in bed for several weeks even after the joint pains have entirely disappeared and till there is no undue quickening of the pulse rate with moderate exercise. *Locally* to the joints f. 384, 385 : lin. methyl salicylate, p. 543 : f. 425. *Internally*, see p. 545 : f. 386, 387 : also ca-acetosalicylate, p. 546. To tonsils, f. 66, 92, 268, 285 : penicillin lozenges, p. 372.

Rhinitis.—*Acute*, See Coryza. *Chronic*, look for the cause : *Locally*, f. 163, 448, 449. Privine-cibazol, p. 364, 636 : endrine, p. 627.

Rickets.—Sunlight, ultra-violet rays ; Also Ca., p. 273, 275 and f. 193, 195, 196. Calciferol, p. 283 and Cod Liver Oil, p. 286 ; Halibut liver oil, p. 285 and other vitamin D products, p. 286. The softened bones should be splinted. Proper attention to digestive system : food should contain adequate vitamin D.

Ringworm.—*Locally*, pyrogallie acid, p. 146 : also f. 111, 303, 383, 478. Dithranol, p. 184 : *Internally*, thallium acetate, p. 185. For tinea cruris, f. 478. X-rays, p. 754.

Scabies.—Open out thoroughly the burrows of the parasites with soap and water and apply, f. 89, 133 to 135, 471. See p. 184 and 679 Change clothes.

Sciatica.—*Locally*, f. 23, 315, 384, 385, 459. *Orally*, f. 376 to 379 ; also see p. 542, 551. *Injection* of 1 to 2% sol. of procaine, p. 598 and alcohol, p. 447 into the nerve trunk. Vitamin B₁, p. 292. Investigate the cause and treat.

Seborrhœa.—Remove scabs by starch poultice or olive oil. Apply, f. 137, 138, 208, 382.

Septicæmia, Streptococcal.—Sulphonamide, p. 363 : specific serum is not now so much used. *Staphylococcal.*—Sulphathiazole, p. 364 : toxoid and vaccine, p. 726. Penicillin, p. 373.

Sinus—Favour drainage. Apply, f. 227, 294 : sulphonamides, p. 364 and penicillin, p. 372.

Small-pox.—*Prophylactic*, vaccination, p. 731. *Locally*, f. 296 : cocoanut oil with camphor (1%). *Orally*, f. 169, 170 ; for mixed infection, sulphathiazole, p. 364.

Sprain.—f. 16, 18, 282, 308, 309 : afterwards f. 67, 213, 384, 385 : infra-red rays and diathermy, p. 755.

Stone, renal.—Plenty of water to drink ; f. 167, 168, 170, 174, 175 and urodonal, p. 707. Also see *Colic*. *Gall-bladder.*—Diet should not contain glandular substances, egg or cream. Regulate bowels, f. 123, 124, 128 : mag. sulph., p. 212 : olive oil, p. 100 Dehydrocholic acid, p. 693 and other bile salt preparations, p. 694. Biliary antiseptics, f. 491. Surgical removal of the stones. Also see *Colic*.

Stomatitis.—Open out the bowels, preferably by castor oil, p. 218. Gargle with f. 27, 31, 54, 56, 57, 81, 86, 103 to 105, 162, 311, 390 and 477. Ulcers are touched with silver nitrate solution 5% or f. 59.

Strongyloidiasis.—Crystal violet, p. 176.

Syncope.—By inhalation, f. 41 ; orally, f. 20, 42, 314, 316, 317, 318, 463 ; intramuscularly, ether, p. 468 ; f. 21, 365, 397, 398, 426, 427 ; also cardiazol and coramine, p. 556.

Syphilis.—*Prophylaxis*, f. 210 also penicillin with aluminium monostearate 4 to 8 lac units, p. 374. *Primary sore*, locally, f. 202, 206 (diluted). Orally, f. 214 to 218 ; also f. 186.

By injection.—Penicillin is the drug of choice, p. 375 ; mercury, p. 308, bismuth, p. 316 and arsenobenzols, p. 327 occupy a subsidiary position.

Sweating of Palm, Sole, Axillæ.—f. 88, 381. *Nocturnal*, f. 392, 437, 446.

Tape Worm.—p. 186, 193 also f. 11, 116, 117.

Tenesmus.—*Orally*, f. 131, 141 ; also spogel seeds, p. 94 ; per rectum, f. 341, 342, 431.

Tetanus.—*Prophylactic*, cauterise the wound with an oxidising agent, p. 151, 153, 259 : tetanus toxoid and serum, p. 727. *Curative* : Serum, p. 727. Sedatives, f. 329 and paraldehyde per rectum, p. 500 : also chloroform inhalation and hypodermically tubocurarine, p. 569 : mephanesin, p. 567 : soluble phenobarbitone, p. 496 : sodium amytal and somnifaine, p. 498.

Tetany.—Improve general health : a plenty of vitamin D containing food, p. 750 along with calcium. In acute tetany calc. gluconate (10%), 10 c.c. or more is given intravenously or intramuscularly, p. 273. In severe cases A.T. 10, p. 284 : parathyroid extract, p. 410 : also sedatives, as bromide, p. 484 and phenobarbitone, p. 496.

Threadworm.—Prevent autoinfection by keeping the fingers clean and soothing anal pruritus, f. 409. Enema of Quassia, p. 199 : Sodium Chloride, p. 244 : sometimes f. 270 : *orally*, Crystal violet, p. 176. Diphenan, p. 191.

Thrombo-angiitis Obliterans.—Drugs of use are vitamin E, p. 287 ; niacin triethanolamine, p. 295 ; depropanex, p. 616 and tetraethylammonium chloride, p. 629.

Thrombosis.—Cerebral, coronary and post operative : heparin, p. 640 : dicoumarol, p. 641. Nicotinic acid, p. 295.

Tonsillitis.—If acute, f. 215 followed by f. 12, 25, 28, 34, 54, 56, 64, 178, 268, 311 : orally, f. 58, 169, 170, 174, 176, 323, 349, 455, 469 : also sulphonamide, p. 366. If chronic, locally, f. 66, 92, 268, 269, 285. Orally, Calcium and vitamins A and D preparations, p. 286. Auto-vaccine sometimes prevents acute exacerbations : surgical removal.

Trypanosomiasis.—*Prophylactic* : suramin, p. 334, 2 g. intramuscularly gives protection for 3 weeks and pentamidine isethionate, p. 333, 200 mg. every 4 to 5 months gives lasting protection. *Curative* : combined treatment of tryparsamide, p. 323, 1.5 g. with suramin 0.5 g. at 5 days' interval : 8 injections in early and 20 in advanced cases or 100 mg. pentamidine isethionate on the 1st day : 200 mg. of it with 1 g. tryparsamide daily for 7 days : general health needs attention.

Tuberculosis of lung.—Rest in bed till the temperature drops and also for some days after. Artificial pneumothorax if the lesion is mostly unilateral and there is recurrent hæmoptysis. *Specifics* : streptomycin, p. 377 and P.A.S., p. 380 are very useful in early caseous type. Calcium, p. 273 and cod liver and halibut liver oil, p. 285. For cough, f. 10, 28, 37, 94, 100, 176, 200, 201, 258, 349, 351, 358, 404, 455, 469, 470, 482, 485. For fever, f. 374 ; as appetizer, f. 18, 119, 181, 312, 347, 399.

Tuberculosis of intestine.—f. 99 and streptomycin, p. 378 and P.A.S., p. 381 : for diarrhoea, f. 51, 191, 230, 231, 347.

Tuberculosis, Miliary.—Streptomycin, p. 377 and P.A.S., 381 are now giving satisfactory results. In *meningeal tuberculosis* these are less effective.

Ulcer foul.—Acriflavine, p. 174 : also f. 60 to 62, 75, 127 and urea, p. 699. Sulphonamide, p. 363 : penicillin, p. 372. *Ulcer chronic*, f. 212, 227, 294.

Ulcer, Bleeding.—f. 49 : *Granulating*, f. 63, 87 also scarlet red ointment, p. 177.

Uræmia.—Purgative, f. 129, 130 or pulv. jalap. co., p. 227. If comatose, mag. sulph. enema, p. 241. Venesection, 6 to 10 oz. of blood esp. if blood pressure is high followed by f. 173, $\frac{1}{2}$ pint or more intravenously and f. 136 orally : sodium lactate, p. 255. If convulsion, lumbar puncture : sedatives even morphia gr. $\frac{1}{4}$. Hypertonic glucose, p. 107. Hot air bath, pilocarpine, p. 576. *Diet*, glucose, lactose, fruit juice, green cocoanut water till the condition improves.

Urticaria.—Open out the bowels, f. 41, 221, 393, 394. Anti-histamines, p. 673. Potassium chloride, p. 252. Milk diet, Ca.,

p. 272, with vitamin D or parathormone also ephedrine, p. 625 : peptone and blood protein, p. 734 : sometimes vitamin K, p. 289.

Vincent's Angina.—Gargle with hydrogen peroxide, p. 151 and f. 55 to 58 : neoarsphenamine locally 20 gr. in 1 fl. oz. and parenterally, p. 328 : penicillin lozenges and procaine penicillin, p. 372 are now more preferred.

Vomiting.—Remove the cause. If due to acute indigestion, wash out the stomach with sod. bicarbonate solution. Gastric sedatives : f. 70, 95, 221, 225, 306, 307, 337, 334, 410, 468.

Weight Reduction.—Thyroid gland, p. 407 : dexedrine, p. 628.

Whooping Cough.—Isolate. Prevent all reflex irritation. Attend to throat. Sedatives as benzyl benzoate, p. 679 : bromoform, p. 486 and f. 323, 349, 351, 352, 358, 375, 436, 469. Specific vaccine, p. 730.

Yaws.—Neoarsphenamine, p. 326 and bismuth, p. 316¹ in 4 to 6 weekly injections : recently, a total dose of 1,200,000 units of procaine penicillin, p. 375 is preferred (a less intensive antisyphilitic treatment).

ADDENDUM 1951 TO BRITISH PHARMACOPŒIA 1948

1. **ÆTHINYLCÆSTRADIOL** (*Æthinylœstradiol*).—Ethinyloestradiol is 17-ethynyl-3 : 17-dihydroxy- $\Delta^{1:3:5}$ -œstratriene.

Prepared by pot. acetylide acting on œstrone in liquid ammonia, evaporation of ammonia, solution in water and precipitation by mineral acid : a fine white inodorous crystalline powder insoluble in water but soluble in alcohol (95%), acetone, chloroform, solvent ether and alkali hydroxides.

Dose, 1/3200 to 1/600 grain or 0.02 to 0.1 mg. daily.

Tabellæ Æthinylœstradiolis, prepared by moist granulation and compression each containing 0.02 mg.

Action.—See p. 397.

2. ANTITOXINA.

Antitoxinum Gas-gangrænosum Compositum (*Antitox. Gas-gangræn. Co.*) replaces Antitoxinum (Edematiens) Compositum.

Antitoxinum Tetanicum : Dose, *Prophylactic*, not less than 1500 units and *Therapeutic*, not less than 50,000 units.

3. **BENZYL PENICILLINUM** (*Benzylpenicil.*).—Crystalline Penicillin G : Penicillin G. : This is the crystalline sodium or potassium salt of the antibiotic prepared by *Penicillium notatum* : 1 mg. has not less than 1550 units of sodium or 1480 units of potassium salt : 85 to 90% of the preparation consists of benzyl penicillin.

4. **PENICILLINUM** p. 368, may be sodium, calcium or potassium salt.

In the pharmacopœial preparations, p. 368, any of the penicillin salts may be used.

Cremor Penicillin (*Crem. Penicil.*) and **Cremor Penicillin Sterilisatus** have 1000 units per g.

Injectio Penicillini (*Inj. Penicil.*), may be prepared with penicillin sodium, calcium or potassium salt or benzyl penicillin sodium or potassium salt. *Strength* if not stated is 200,000 units per ml.

Injectio Penicillini Oleosa (*Inj. Penicil. Oleos.*), may be prepared in the same way as above. *Strength*, if not stated, is 300,000 units per ml.

Oculenta Penicillin may be prepared with any of the above salts of penicillin.

Procainæ Benzylpenicillinum (*Procin. Benzylpenicil.*) is the monohydrate prepared by interaction of procaine hydrochloride and benzyl penicillin : has not less than 950 units of penicillin per mg. and between 37.5 to 40.5% of procaine.

Trochisci have 1000 units in each.

Unguentum Penicillini (*Ung. Penicil.*) has 1000 units per g.

5. **CETRIMIDUM** (*Cetrimid.*) is a mixture of alkylammonium bromides prepared by condensation of cetyl bromide with trimethylamine.

A white or creamywhite voluminous, free-flowing powder with faint characteristic odour and bitter soapy taste : soluble in 10 of water and almost completely in alcohol (95%).

Action.—See p. 102.

6. CHLORAMPHENICOL (*Chloramphen.*),Chloromycetin, $C_{11}H_{12}O_5N_2Cl_2$.

Prepared by the growth of *Streptomyces venezuelæ* or synthetically. Fine white, greyish or yellowish white crystals, needles or elongated plates, slightly soluble in water but freely in alcohol (95%): taste is bitter.

Action.—See p. 378.

7. DICOPHANUM (*Dicophan.*), D.D.T., $C_{14}H_9Cl_5$.

Dicophane, mainly is 1:1:1-trichloro-2:2-di (*p* chlorophenyl) ethane, prepared by sulphuric acid acting on a mixture of chlorobenzene and chloral or chloral hydrate: white crystals, powders or granules, inodorous or with a slight aromatic odour.

Action.—See p. 194.

8. STREPTOMYCIN, See p. 376.

Dihydrostreptomycinum (*Dihydrostreptomyc.*), by hydrogenation of streptomycin is made into hydrochloride, $C_{21}H_{41}O_{12}N_7 \cdot 3HCl$ and sulphate ($C_{21}H_{41}O_{12}N_7$), $3H_2SO_4$.

Streptomycini et Calcii Chloridum (*Streptomyc. et Calc. Chlorid.*) is the calcium chloride double salt, $(C_{21}H_{39}O_{12}N_7 \cdot 3HCl)_2 \cdot CaCl_2$.

Streptomycini Hydrochloridum (*Streptomyc. Hydrochlor.*) is the hydrochloride, $C_{21}H_{39}O_{12}N_7 \cdot 3HCl$ and Streptomycini Sulphas (*Streptomyc. Sulph.*), $(C_{21}H_{39}O_{12}N_7)_2 \cdot 3H_2SO_4$.

White solid (except hydrochloride which is powder), very soluble in water and contain not less than 600 units per mg.: when streptomycin hydrochloride or sulphate is asked for, streptomycin et calcium chloride is supplied.

Dose is according to the need of the patient.

Injectio with any of the above four: one ml. contains 250,000 units.

Dose, according to the need of the patient.

9. DIMERCAPROL (*Dimercap.*), British Anti-Lewisite, B.A.L. is 2:3-dimercaptopropanol, $CH_2(SH) \cdot CH(SH) \cdot CH_2OH$.

Prepared by brominating allyl alcohol and treating 2:3 dibromopropanol formed with sodium hydrosulphide, containing between 98.5 to 101.5% of the active substance: a colourless or slightly yellow clear liquid with alliaceous odour: soluble at 15° in 16.7 of water.

Action.—See p. 312.

10. INDICARMINUM (*Indicarmin.*), Indigo carmine, $C_{16}H_8O_8N_2S_2Na_2$.

Indigo Carmine, disodium indigotin-5:5'-disulphonate is prepared by the action of sulphuric acid on indigotin, neutralisation with sod. bicarb. and precipitation with sod. chlor: contains not less than 90% of $C_{16}H_8O_8N_2S_2Na_2$ dried at 100°: soluble in 100 of water, more in hot water but precipitated by sodium chloride.

Dose, $\frac{3}{4}$ to $1\frac{1}{2}$ grains or 0.05 to 0.1 gramme, subcutaneously: $\frac{1}{8}$ to $\frac{1}{4}$ grain or 8 to 16 mg. intravenously.

Action.—See p. 236.

11. ISOPRENALINÆ SULPHAS (*Isoprenal. Sulph.*), Isoprenaline Sulphate, $C_{11}H_{17}O_3N \cdot \frac{1}{2}H_2SO_4 \cdot H_2O$.

Isoprenaline sulphate, 1-(3:4-dihydroxyphenyl)-2-isopropyl amino-ethanol sulphate, prepared by condensing isopropylamine with chloroacetocatechol, reducing and making sulphate: contains 5.3 to 5.5% of N.

and 6 to 6.3% of S. A colourless inodorous, crystalline powder, soluble in of water but insoluble in alcohol (95%), chloroform and in solvent ether. Dose, $\frac{1}{6}$ to $\frac{1}{2}$ grain or 10 to 30 mg.

Action.—Isoprenaline has adrenaline action on the small blood vessels and the bronchioles causing **vaso-constriction** and **bronchodilatation**. It is available in various trade names (see p. 623) and 10 mg. tablets are used as *linguets* or 1% aqueous solution as *spray* also *orally* in bronchial asthma, often causing more intensive and lasting effect.

12. MEPYRAMINÆ MALEAS (*Mepyramin. Maleas*), Mepyramine Maleate, $C_{21}H_{27}O_5N_3$.

Mepyramine Maleate is the acid maleate of *N*-*p*-methoxybenzyl-*N'*-*N'*-dimethyl-*N*-2-pyridylethylene diamine, prepared by condensing 2-*p*-methoxybenzyl-aminopyridine with 2-dimethyl-amino-ethyl chloride in the presence of sodamide : contains 98.5 to 101% of $C_{21}H_{27}O_5N_3$.

A nearly inodorous white or creamy white powder with bitter taste, soluble at 20° in 0.5 of water, 2.5 of alcohol (95%) and 1.5 of chloroform.

Dose, 5 to 12 grains or 0.3 to 0.8 gramme, daily in divided doses.

Action.—Mepyramine maleate commercially known as *Anthisan* or *Neo-antergen* is antihistaminic : See p. 673.

13. METHACHOLINÆ CHLORIDUM (*Methacholin. Chlorid.*), $C_8H_{18}O_2NCl$.

Methacholine chloride is acetyl-beta-methylcholine hydrochloride prepared by acetylation of beta methylcholine hydrochloride containing between 21.6 to 22.3% of CH_3CO and between 17.8 to 18.4% of Cl, dried at 105° for 4 hours. Colourless or white crystals or powder nearly inodorous and very deliquescent : very soluble in water, alcohol (95%) and in chloroform.

Dose, $1\frac{1}{2}$ to 3 grains or 0.1 to 0.2 gramme : $\frac{1}{6}$ to $2\frac{1}{5}$ grain or 10 to 25 mg. subcutaneously.

Action.—Methacholine chloride, available as *Mecholyl chloride* or *Amecol* has cholinergic action : See p. 590.

14. OXOPHENARSINÆ HYDROCHLORIDUM (*Oxophenarsin. Hydrochlor.*), $C_6H_5O_2NAs, HCl$.

Oxophenarsine Hydrochloride, *Mapharside*, is 3-amino-4-hydroxyphenylarsine oxide hydrochloride, prepared by reducing 3-amino-4-hydroxyphenylarsenic acid with KI and SO_2 in acid solution : contains between 29.5 to 32% of trivalent arsenic : 14.8 to 16% of chloride, substance being dried over phosphorus pentoxide. A white inodorous powder, soluble in water, alkali hydroxides and carbonates solution and in dilute mineral acids.

Dose, $\frac{1}{2}$ to 1 grain or 20 to 60 mg. intravenously.

15. OXOPHENARSINÆ TARTRAS (*Oxophenarsin. Tart.*), $C_6H_5O_2NAs, C_4H_6O_6, 2H_2O$.

Oxophenarsine Tartrate, hydrogen tartrate of 3-amino-4-hydroxyphenylarsine oxide, prepared by reducing 3-amino-4-hydroxyphenylarsenic acid with KI and SO_2 in acid solution : contains between 19 to 19.6% of trivalent arsenic and not more than 19.6% of total arsenic. White inodorous powder soluble in 25 of water and in alcohol 95% and alkali hydroxides and carbonates and dilute acid solution.

Dose, $\frac{3}{4}$ to $1\frac{1}{2}$ grain or 45 to 90 mg. intravenously.

Action. See p. 328.

16. PHENIODOL (*Pheniodol*), $C_{15}H_{12}O_3I_2$.

Pheniodol, beta(4-hydroxy-3 : 5-diiodophenyl)- α -phenylpropionic acid, prepared by reduction of beta-*p*-methoxyphenyl- α -phenyl acrylic acid, its demethylation and iodination : contains between 50.5 to 51.5% of I.

A creamy-white powder with slight odour and producing a tingling sensation in the mouth. Soluble in aqueous alkaline solution and in alcohol 90% but not in water.

Dose, 45 to 90 grains or 3 to 6 grammes : single dose.

Action.—See p. 232.

17. PHENOLSULPHONPHTHALEINUM (*Phenolsulphonphthal.*), Phenol Red, $C_{19}H_{14}O_5S$.

Phenolsulphonphthalein is prepared by fusing *o*-sulphobenzoic acid with phenol at about 130° : contains not less than 94% of $C_{19}H_{14}O_5S$. A bright or darkred, inodorous, crystalline powder, soluble in about 1300 of water but readily in alkali hydroxides and carbonates.

Dose, 1, 10 grain or 6 mg. intramuscularly or intravenously.

Action.—See p. 236.

18. PROGUANILI HYDROCHLORIDUM (*Proguan. Hydrochlor.*) $C_{11}H_{16}N_5Cl$, HCl.

Proguanil Hydrochloride or *Paludrine* is the hydrochloride of N¹-*p*-chlorophenyl N⁵-isopropyldiguanide, prepared by interaction of *p*-chlorophenyldicyandiamide with isopropylamine hydrochloride containing 98% of $C_{11}H_{16}N_5Cl$, HCl. An inodorous crystalline powder with a bitter taste : soluble in 110 of water (more in hot water) and soluble in 37 of alcohol (95%).

Dose, 1½ to 6 grains or 0.1 to 0.4 gramme, daily.

Tabellæ Proguanili Hydrochloridi, each tablet if not otherwise stated, contains 0.1 g. *Dose*, as of proguanil hydrochloride.

Action.—See p. 348.

19. PROMETHAZINÆ HYDROCHLORIDUM (*Promethazin. Hydrochlor.*), $C_{17}H_{21}N_2S$ Cl.

Promethazine hydrochloride is the hydrochloride of *N*-(2-dimethylamino-*n*-propyl) phenothiazine, prepared by condensation of phenothiazine with 2-chloro-1-dimethylaminopropane in the presence of sodamide : contains between 10.8 to 11.2% of Cl and between 8.5 to 8.9% of N, the substance being dried at 100°.

Dose, 2½ to 1½ grain or 25 to 75 mg.

Action.—See p. 673.

20. PROPYLTHIOURACILUM (*Propylthiouracil.*), $C_7H_{10}ON_2S$.

Propylthiouracil is 4-hydroxy-2-mercapto-6-*n*-propylpyrimidine prepared by condensation of ethyl betaketohexoate with thiourea : contains not less than 98% of $C_7H_{10}ON_2S$, substance being dried at 100°. White or pale cream, inodorous crystalline powder with bitter taste : almost insoluble in water, soluble in alkali hydroxide solution.

Dose, 2½ to 1½ grain or 25 to 100 mg.

Tabellæ Propylthiouracili : each tablet unless otherwise stated, contains 25 mg.

Action.—See p. 409.

21. QUINALBARBITONUM SODIUM (*Quinalbarbiton. Sod.*), $C_{12}H_{17}O_3N_2Na$.

Quinalbarbitone sodium, *Seconal Sodium* is monosodium of 5 allyl-5 1-methylbutyl) barbituric acid, prepared by the interaction between

alcoholic solution of quinalbarbitone with sodium ethoxide; contains 98 to 100·5% of $C_{12}H_{17}O_3N_2Na$ being dried at 100°.

Dose, $\frac{3}{4}$ to 3 grain or 50 to 200 mg

Action.—See p. 498.

22. SODII CITRAS ACIDUS (*Sod. Cit. Acid.*), Disodium Hydrogen Citrate, $C_6H_6O_7Na_2, 1\frac{1}{2} H_2O$.

Sodium Acid Citrate is prepared by the interaction of citric acid and sodium carbonate, containing between 98 to 104% of the substance: white inodorous powder with saline taste. Soluble in less than 2 of water and insoluble in alcohol (90%).

Action.—See p. 256.

23. SULPHADIMIDINA (*Sulphadimidin.*), $C_{12}H_{14}O_2N_4S$.

Sulphadimidine or *Sulphamerazine* is 2-(*p*-aminobenzene sulphonamido)-4:6-dimethyl-pyrimidine, prepared by condensation of *p*-acetamidobenzene sulphonyl chloride with 2-amino-4:6-dimethylpyrimidine and hydrolysis: contains 99 to 101% of the substance.

Dose, 30 grains or 2 gramme initially and 15 grains or 1 gm. every six hours.

Tabellæ have the same dose.

Sulphadimidina Sodium (*Sulphadimidin. Sod.*), $C_{12}H_{13}O_2N_4SNa$.—Prepared by the interaction of alcoholic solution of sulphadimidine and aqueous solution of sodium hydroxide. It contains between 98 to 101% of $C_{12}H_{13}O_2N_4SNa$.

Dose, 15 to 30 grains or 1 to 2 gm. intravenously.

Action.—See p. 376.

24. TUBOCURARINÆ CHLORIDUM (*Tubocurar. Chlorid.*), *d*-Tubocurarine chloride, $C_{38}H_{44}O_6N_2Cl_2 \cdot 5H_2O$.

Tubocurarine chloride is the chloride of an alkaloid *d*-tubocurarine obtained from the plants of the genus *Chondrodendron* having the specific biological activity of curare on neuromuscular transmission: contains not more than 9% of methoxyl, CH_3O in the substance dried at 100°. A white inodorous microcrystalline powder sparingly soluble in water and in alcohol (95%), more soluble in warm water and in alkali hydroxide solution.

Dose, according to the need of the patient.

Action.—See p. 567.

25. VACCINUM TYPHO-PARATYPHOSUM A, B et C (*Vaccin. Typho-paratyphos. A, B and C*), T.A.B.C. Vaccine.

Typhoid-paratyphoid-A, B and C vaccine is the sterile suspension of *S. typhi*, *S. paratyphi* A, *S. paratyphi* B and *S. paratyphi* C. Contains in 1 ml. 1000 million typhoid bacilli, 500 to 750 million each of paratyphoid A, B and C.

Dose, *Alcohol-treated* vaccine, initially 0·25 ml. second dose after 7 to 28 days, 0·5 ml. *Vaccine other than alcohol-treated*: initially 0·5 ml. and second dose after 7 to 28 days, 1 ml. Dose of T.A.B. Vaccine is the same.

Action.—See p. 729.

26. VANILLINUM (*Vanillin.*), Vanillin, $C_8H_8O_3$.

Vanillin is 4-hydroxy-3-methoxybenzaldehyde obtained from *Vanilla planifolia* and other species of *vanilla* or prepared synthetically. White or cream coloured crystalline needles or powder with characteristic odour and taste of vanilla.

Action.—Vanillin is used as a flavouring agent and in perfumery. *Ethylvanillin*, 4-hydroxy-3-ethoxy benzaldehyde is a more powerful flavouring agent.

HUMAN BLOOD PREPARATIONS (See p. 734)

(i) *Whole Human Blood* : See p. 734.

(ii) *Concentrated Human Red Blood Corpuscles*.

Prepared from one or more preparations of whole human blood not more than 7 days old, directly matched with the blood of the recipient from which for concentration not less than 40% of total fluid is removed.

(iii) *Dried Human Plasma*.

The supernatant fluid pool separated from blood which is cross-neutralised against hæmagglutinins, is dried avoiding denaturation of the protein : when dissolved in water contains 4.5% w/v of protein.

(iv) *Liquid Human Serum*.

The pool of fluids separated from blood withdrawn from human subjects after clotting, is cross neutralised of hæmagglutinins by suitable admixture of different blood groups. This contains 6.5% w/v of protein.

(v) *Dried Human Serum*.

Liquid Human serum is freeze-dried to avoid denaturation of the proteins : when dissolved in water of the same volume from which it is prepared, it contains 6.5% w/v of protein.

(vi) *Human Fibrinogen*.

Prepared from liquid plasma by precipitation with organic solvent under controlled pH, ionic concentration and temperature : this on addition of thrombin is made into fibrin.

(vii) *Human Fibrin Foam*.

A dry artificial sponge of human fibrin is prepared by clotting with thrombin a foam of a solution of human fibrinogen : frozen foam is dried and sterilised by dry heat.

(viii) *Human Thrombin*.

The enzyme which converts fibrinogen into fibrin, is obtained from human plasma by precipitation with salts and organic solvents under controlled pH, ionic concentration and temperature. It has not less than 10 clotting doses per mg.

Action.—(i) *Whole blood* is used for transfusion to replace red blood corpuscles, platelets, clotting factors and other normal blood constituents missing in the patient and to restore the blood volume : adequate compatibility test is performed before transfusion.

(ii) *Concentrated human red blood corpuscles* are used in the treatment of anæmias and the hæmoglobin value may be raised by about 15% by the red blood corpuscles obtained from 1080 ml. of whole blood.

(iii) *Dried Human Plasma*, reconstituted by adding isotonic solution of dextrose and NaCl is used for liquid plasma. See p. 735.

(iv) *Liquid Human Serum* is used in the same way as human plasma. See p. 735.

(v) *Dried Human Serum* is used in the same way as dried human plasma.

(vi) *Human Fibrinogen* is used in surgery along with human thrombin to fix nerve sutures (2% solution) and help adhesion of skin and mucous membrane grafts (1 to 2% solution). It is also used in the preparation of human fibrin foam.

(vii) *Human Fibrin Foam* is used along with human thrombin as hæmostatic in brain and lung surgery. A piece of the foam is saturated in human thrombin dissolved in injection of sodium chloride and placed on the bleeding points : immediate coagulation takes place.

(viii) *Human Thrombin* is used along with human fibrinogen and fibrin foam : the strength of the solution depends on the rapidity of clotting needed.

1951 AMENDMENTS TO 1948 PREPARATIONS

1. *Aneurinæ Hydrochloridum*.—Dose changed : *prophylactic*, 1/30 to 1/12 grain or 2 to 5 mg. : *therapeutics*, $\frac{1}{3}$ to $\frac{3}{4}$ grain or 20 to 50 mg. daily and this is the dose of *Tabellæ aneurinæ hydrochloridi*, each tablet containing 3 mg. : for *Injectio*, the therapeutic dose is adopted as above.

2. *Dienæstrol* and its *Tabellæ*.—Dose, 1/60 to 1/12 grain or 1 to 5 mg. daily.

3. *Digitalis Præparata* and *Tinctura*.—80 mg. to be changed to 76 mg.

4. *Injectio Nicotinamidi*.—Dose, $\frac{3}{4}$ to 4 grains or 50 to 250 mg. and each ml. contains 50 mg. or $\frac{3}{4}$ gr. in 15 min.

5. *Injectio Quininæ Dihydrochloridi*.—If the strength is not stated, it is 0·3 grm. in 1 ml. or 5 gr. in 15 min.

6. *Injectio Sodii Chloridi*.—Synonyms are Physiological solution of sodium chloride for injection, Physiological saline solution for injection and Normal saline solution for injection.

Injectio Sodii Chloridi Composita.—Synonym is Compound solution of sodium chloride for injection.

7. *Methylthiouracilum* contains not less than 98% and *tabellæ* between 88 to 110% of the substance. Dose, $\frac{3}{4}$ to 3 gr. or 0·05 to 0·2 grm.

8. *Paraffinum Molle Album* and *Paraffinum Molle Flavum* : alternate names are White Petroleum Jelly and Yellow Petroleum Jelly.

9. *Pethidine* (p. 521) : *Tabellæ Pethidinæ Hydrochloridum*. Dose, $\frac{2}{5}$ to $1\frac{1}{2}$ gr. or 25 to 100 mg.

10. *Suraminum* contains not less than 95% of the substance dried at 130°.

11. *Theophyllina cum Æthylenediamina*.—It contains between 75 to 82% of anhydrous theophylline and 12·3 to 13·8% of ethylenediamine. Its *tabellæ* have 67·5 to 90% of theophylline and 11·1 to 15·2% of ethylenediamine : each contains 0·1 g.

12. *Purified Toxoid*, Aluminium Phosphate Precipitated, prepared by adding purified Formol Toxoid to hydrated aluminium phosphate in suspension in injection of sodium chloride replaces Diphtheria Toxoid-antitoxin mixture (p 723). Dose, 0·5 ml twice with intervals of not less than 4 weeks.

13. *Tuberculin Derivativum Proteinicum Purificatum* is standardised, each ml. containing 100,000 units of old tuberculin.

Dose, 1, 10 or 100 units in each 0·1 ml. intradermally.

Tuberculinum Pristinum has also the same standardisation and dose.

BIOLOGICAL STANDARD AMENDMENT (See p. 23)

| Standard Preparation. | Nature. | Unit in mg. | Relation to international unit. | Form in which issued. |
|--|-----------------------------------|-------------|---|---------------------------------|
| Diphtheria antitoxin for flocculating test | Frozen anti-toxic serum | — | Assayed in terms of international standard. | 100 units/ml. |
| Digitalis | Dried powder. | 76 | identical. | 2·5 g. in sealed ampoule. |
| Dihydrostreptomycin | as sulphate. | 0·001307 | — | 25 mg. in sealed ampoule. |
| Dimercaprol | Pure product | — | — | 3 mg. in sealed ampoule. |
| d-Tubocurarine chloride | Pure crystallin substance. | 1·0 | — | 5 mg. in sealed ampoule. |
| Serum, Anti-A blood grouping | Dried anti-serum. | 0·3465 | identical. | sealed ampoule having 256 unit. |
| Serum, Anti-B blood grouping | Dried anti-serum. | 0·3520 | identical. | as above. |
| Streptomycin | as sulphate. | 0·00128 | — | 20 mg. in sealed ampoule. |
| Tetanus antitoxin | Dried antitoxin | 0·3540 | identical. | 10 units/ml. |
| Tuberculin. old | Glycerin solution. | 0·0001 ml. | identical. | International potency. |
| Vitamin A | Pure vitamin A acetate. | 0·000344 | identical. | 10,000 units/g. |
| Vitamin D | Pure crystalline D ₃ . | 0·000025 | identical. | 1000 units/g. |

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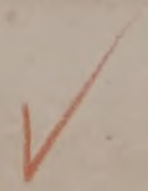
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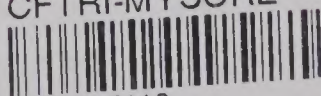


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